AUGUST 1950

BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

Original Articles

by

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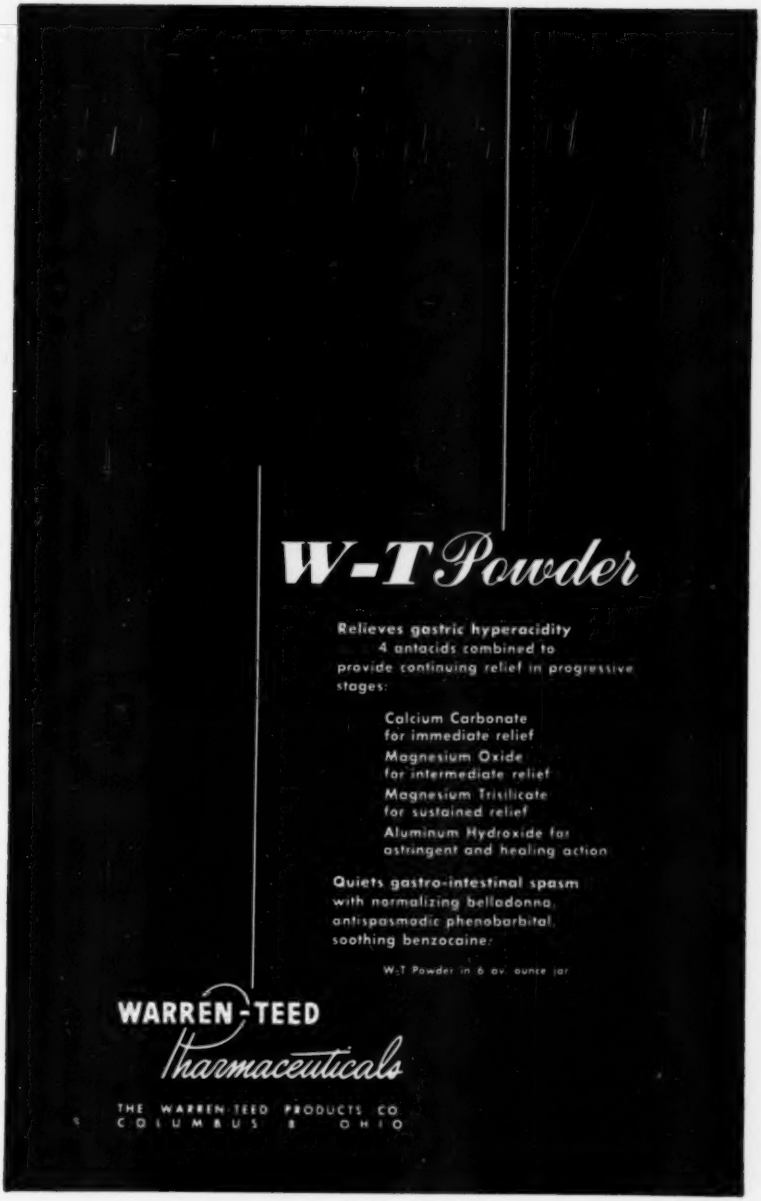
SECTION ON MICROBIOLOGY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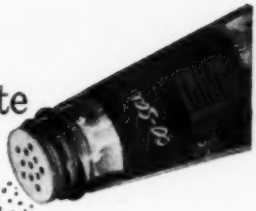

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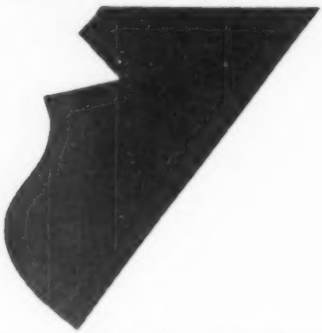

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1. Friedlaender & Friedlaender: Amer. Pract. 2:643, June, 1948

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Abstract from Gastroenterology
Vol. 13, No. 4, October 1949

A METHOD OF IMPROVING FUNCTION OF THE BOWEL

J. ARNOLD BARGEN, M.D.,
Division of Medicine, Mayo Clinic, Rochester, Minnesota

Constipation, probably the commonest of physical complaints, may be caused by several factors, singly or combined: *1.* nervous fatigue and nervous tension; *2.* improper intake of fluid; *3.* improper dietary habits; *4.* failure to heed the call to stool; *5.* lack of exercise, and *6.* excessive use of laxatives.

It would seem logical that correction of constipation lies in the suitable adjustment of these factors.

Any diet for relief of constipation must supply material which has limited absorption in the small intestines and which adds bulk in the colon, i.e., fruits and vegetables. Daily fluid intake, from 2.5 to 3.5 liters, is highly important. Since many people find it difficult to eat enough dietary bulk, the trend recently has been toward hydrophilous colloids.

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Case 2. Nun, age 69.—Obstinate constipation of lifelong duration. *After treatment:* In about a week . . . soft stools.

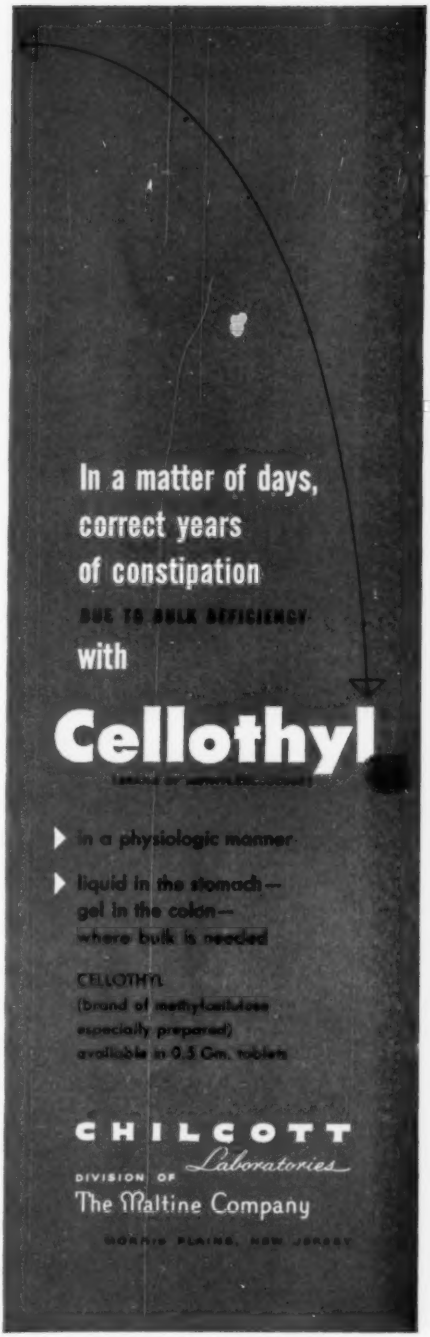
Case 3. Man, age 44.—Constipated many years; severe diabetes. *After treatment:* Normal stools at the end of one week.

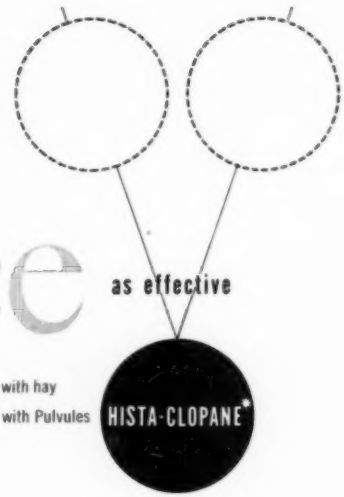
Case 4. Woman, age 62.—Very difficult evacuation after carcinoma removal. *After treatment:* She passed her stools without discomfort.

Case 5. Woman, age 19.—Obstinate constipation; she had taken a laxative almost daily since early childhood. *After treatment:* At the end of two weeks she was passing stools daily.

COMMENT

Function of the bowel can be greatly improved by the addition of methylcellulose, appropriately prepared (Cellothyl). It represents a valuable addition to the well-ordered program of medical care.





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SECOND SERIES AUGUST 1950 VOL. 26, NO. 8

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MAITLON ASHFORD, *Editor*

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

VOL. 26, NO. 8 AUGUST 1950

ANTI-MICROBIAL THERAPY IN PULMONARY TUBERCULOSIS: MEDICAL ASPECTS*

CARL MUSCHENHEIM

Attending Physician, The New York Hospital

THE clinically most effective anti-bacterial therapy of pulmonary tuberculosis is that with streptomycin and its derivative dihydrostreptomycin. My remarks will therefore deal mainly with the use of these drugs. There are, however, other agents which have come into use in the past several years; and no discussion of the present status of treatment could be complete without considering these also. Hence the rather broad title selected for our presentation this evening.

It is a somewhat artificial separation to divide the subject into its medical and surgical aspects, since neither can be considered strictly apart from the other. It is inevitable, therefore, that I shall encroach somewhat on Dr. Chamberlain's part of the program, and I trust that he will discuss some of the medical aspects from the surgeon's point of view.

I should like to remind you that it is now just over five years since streptomycin was first given to patients with pulmonary tuberculosis

* Read before Sections on Surgery and Medicine, Combined Meeting, January 6, 1950, New York Academy of Medicine.

TABLE I

Clinical Type	No. of cases	Early Result: Cavity Closure	Early Result: Sputum conversion	Follow Up: Arrested without collapse	Follow Up: Arrested with collapse	Follow Up: Active without collapse	Follow Up: Active with collapse	Follow Up: No follow-up	Follow Up: Dead
I. Early Predominantly exudative									
a) Patchy pneumonic	16	9	9	5	5	3	1	1	1
b) Confluent pneumonic	6	2	3	1	3		1		1
c) Progressive primary	1	1	1	1					
d) Caseo-cavernous	6	0	0						6
	29	12	13	7	8	3	2	1	8
II. Chronic type with fibrocavernous secondary changes	38	7	11	9	9	4	11		5
Total	67	19	24	16	17	7	13	1	13
Far Advanced	44								
Mod. Advanced	22								
Minimal	1	(Treatment directed to complicating Bronchial Tuberculosis)							

by Hinshaw and his co-workers. Since then a vast literature has accumulated which it would be impossible to attempt to review. Most of the reports that have been published are concerned with the immediate and early results and there are still few reports on follow-ups of more than one year. It is indeed difficult to assess the long term results of streptomycin in pulmonary tuberculosis therapy, since it is never properly employed as an independent treatment but always as an adjuvant. Last summer, Dr. John McClement assembled and analyzed all of the follow-up records of 67 consecutive patients treated at the New York Hospital between April 1946 and December 1947, with a follow-up period of one and a half to over three years and an average of twenty-six months. I should like to show some of the tabulations that he made, because I think that they permit us to draw some conclusions, at least, concerning how the long term results in pulmonary tuberculosis are influenced by streptomycin therapy.

Table I shows the over-all picture with the cases divided into various categories of clinical types. Since virtually all of these cases were

of moderately or far advanced extent they are not grouped according to the stage, but rather according to the presumed pathological character, so far as this could be deduced from clinical and x-ray observations. There are two main groups: 1) the relatively early and predominantly exudative types with caseation and early excavation but apparently little fibrosis, and 2) the chronic type with more advanced fibro-cavernous secondary changes. Group 1 is further broken down into the *patchy pneumonic* with thin-walled early cavities, the *confluent pneumonic* including principally the confluent tuberculous pneumonias with little or no demonstrable excavation, one case of *progressive primary* disease (with cavitation), forming a solitary instance in this category, and finally the fulminant type of massive caseation with large cavities but little evidence of fibrosis which we have designated as the *caseo-cavernous* type. The second and third columns show what were the results at the end of treatment in terms of cavity closure and sputum conversion. A glance at the table reveals that these objectives were attained, as might be expected, in a considerably larger proportion of the early predominantly exudative, among which cavities disappeared in nearly half (12 of 29), than in the chronic type of which less than one-fourth (7 of 38) achieved apparent cavity closure. Sputum conversions ran a little bit higher in both groups, but these could scarcely be permanent where obvious cavitation persisted. The greatest number proportionally of closures and conversions were in the patchy pneumonic group in which the least secondary changes of any kind (such as caseation, excavation and fibrosis) had occurred. Here the early results were favorable in over half (9 of 16). Despite these early favorable results, however, we see (in looking over on the follow-up side) that only 5 of the 16 could be classified as arrested without collapse therapy. In 5 more collapse therapy was required to achieve lasting control, 3 are active without collapse therapy for which they were unsuitable, one is active despite having received collapse therapy and one is dead. These cases were for the most part considered unsuitable for collapse therapy before they received streptomycin either because of the acuteness or the extent of the disease. Bearing this in mind, the total of 10 cases classifiable as arrested on late follow-up is probably better than would have been expected (even in this most favorable subdivision) by bed rest and collapse therapy alone. I say probably, since there is no precise standard of comparison. When we come to

TABLE II

Clinical Type	*No. Cases*	*Present Status* *Arrested without collapse*	*Arrested but had early collapse*	*Arrested without collapse but had one relapse*	*Active After a relapse*	*No follow-up*	*Dead*
I. Early predominantly exudative	8	4	1	1	2		
a) Patchy pneumonic							
b) Confluent pneumonic	2	1					1
c) Progressive primary	1	1					
d) Caseo-cavernous	0						
II. Chronic type	8	6			2		
Total	19	12	1	1	4		1

the next sub-group of 6 patients with acute confluent tuberculous pneumonias, all with frank signs of consolidation, the late results are more unequivocably favorable since we have 5 survivals, of whom 4 are actually arrested, in a category in which formerly we anticipated a 50 to 75 per cent mortality. Passing over the progressive primary, of which there is only one case, we come to the least favorable group of all, namely, the caseo-cavernous in which there were no favorable early results and no late survivals. Finally, in Group 2, the cases which displayed evidence of considerable chronicity, the late results are in one way rather more favorable than might have been anticipated from the early results since more patients (9) finally became arrested without the aid of collapse therapy than the 7 who had shown immediate cavity closure. Of those who received subsequent collapse therapy slightly less than half (9 of 20) have become arrested. Altogether in the entire series, with and without collapse therapy 33 cases are arrested (exactly 50 per cent excluding the one case lost to follow-up).

Although the number of patients here represented is relatively small the over-all mortality of 13 out of 67 (or slightly less than 20 per cent), while not small, is in my judgment considerably reduced from what formerly would have been expected with cases of this severity. In the period under discussion the administration of streptomycin was practically restricted in this clinic to cases considered to have had a bad prog-

TABLE III

COLLAPSE OR RESECTION PROCEDURES	*Treated*	*Arrested*
Pneumothorax (excluding anatomically unsuccessful)	8	5
Thoracoplasty (13 primary)	16	11
Revision Thoracoplasty	1	0
Pneumonectomy	1	1
Lobectomy	1	0
Pneumoperitoneum	3	0
Total	30	17

nosis with standard treatment. When the mortality of the far advanced cases alone is considered, it is still under 30 per cent, which is probably also a favorable figure considering the composition of the series.

Turning now to a special consideration of the patients who both closed cavities and converted sputum during streptomycin treatment, we see that of the 19 in this originally favorable group, 12 have become arrested without collapse therapy having been used. The majority, therefore, have consolidated the early advantage. One case only was given collapse therapy merely on the basis that a relapse was feared. Six patients relapsed of whom one has died. These results, despite the relatively small number of cases are, I believe, significant and indicate that patients showing a good immediate response to streptomycin, need not as a general rule have collapse therapy to protect them from early relapse as has been advocated by some. Prolonged bed rest is, however, most important in the after-care and we were fortunate in being able to provide this for most of these patients, either in our own hospital or in sanatoriums. The one death, incidentally, was in a patient who had originally made a spectacular recovery from a tuberculous pneumonia of more than lobar extent, but who had not accepted suitable after-care. The relapse occurred a year later with a streptomycin-fast rapidly progressive pulmonary tuberculosis.

In the foregoing discussion I have referred for convenience to collapse therapy when I should have spoken of collapse or resectional therapy, since one patient had a lobectomy and one a pneumonectomy. The distribution of procedures is shown in Table III.

This tabulation is of particular interest in estimating how the advent of streptomycin has influenced the use of collapse therapy. The 30 patients who received it represent a little over 40 per cent of the total. Since the over-all use of collapse therapy in the past has been generally between 30 and 50 per cent, it appears that the use of streptomycin has not diminished the proportion. In this particular group of patients I should estimate that the proportion is high, since many especially among the earlier cases were desperately ill, and would formerly not have been regarded as fair risks for these procedures.

Discussion

These few numerical data have not been presented as proof that streptomycin has value. That it has a demonstrably favorable immediate effect in most cases of pulmonary tuberculosis, and especially so on the acute manifestations, is generally accepted and there is a considerable body of statistical evidence which justifies this acceptance. What I believe is significant in this follow-up analysis is that it reveals the pattern of the late results. On the whole I should regard this pattern as encouraging, although with only 50 per cent of the cases arrested despite a relatively free use of collapse procedures it cannot be claimed that it is brilliant. It is encouraging, however, that the patients who showed particularly good early responses have, for the most part, fared well subsequently.

Without individually reviewing each case one cannot convey the over-all impression which we have ourselves gained from the study of these patients. Since it is merely in the category of clinical impressions I shall but mention it for what it is worth. This is that the disease, except in the most fulminating cases, generally pursues a more indolent course after therapy than it did before even when it has not become arrested. The converse, that the disease takes on a more fulminating character after therapy than it had before, has not been observed in a single instance.

The 67 cases of which I have spoken were all treated with regular streptomycin, but on varying regimens. Over half were treated with one gram a day for forty-two days, the others (who were earlier in the series) with 3 grams daily for either 120 days or forty-two days. Of those treated on the forty-two days regimen twenty-two (or approximately one-third) were re-treated. With but one or two excep-

tions, re-treatment was ineffectual, and associated with *in vitro* evidence of bacterial resistance early in the second course.

This brings up the paramount question of how best to use streptomycin today, either alone or in combination with other antimicrobial agents. Here my conclusions must be based not alone on first hand experience but on the collective experience reported from many clinics. We have, with our relatively small facilities, had too few patients to carry out comparative regimen studies, but such studies are being conducted systematically on a coöperative basis by various groups, most successfully perhaps in the Veterans Administration.

These have shown that an extraordinarily wide latitude in dosage and frequency of administration is compatible with clinically appreciable response. Daily doses varying from 0.5 gm. to 2.0 gm. and more have been reported to produce improvement so nearly equal in degree that there is no agreement as to the superior benefit of the larger doses as determined by direct clinical observations. When the drug is administered daily, there is certainly no observable difference between divided and single dose regimens, but more than 1.0 gram is impractical to give in a single injection. Regimens consisting of treatment given only every three days or twice a week, instead of daily, are reported to produce good responses and may have certain advantages which I shall mention presently. As to total duration the standard courses in investigative programs have been principally of the relatively short forty-two or sixty days variety or the long ninety or 120 days schedules. We were, I believe, the first to use the forty-two day course but we discontinued it some time ago, because accumulating knowledge about the emergence of resistance indicates that this is a particularly disadvantageous selection. The Veterans Administration Hospitals report[1] in a series of over 1000 patients that 50 per cent become predominantly resistant at the end of two months of therapy. In the forty-two days regimen, by continuing half way into the second month, the purpose of a short course, namely to preserve an opportunity to later resume effective therapy if needed, is greatly compromised. Actually the very cases which may require more therapy are most likely to be in the resistant group, since several studies[2, 3] have shown that the cases with more extensive caseation and cavitation usually become drug-fast the most rapidly.

In order to select a rational scheme of antimicrobial therapy in pulmonary tuberculosis and to correlate this effectively with surgical

measures, three principal factors must be taken into consideration. These are: 1) the toxicity of the therapeutic agent or agents, which factor governs the selection of the particular preparations to be used and the permissible range of dosage; 2) the existence and rapidity of development of drug fastness, governing the duration and the frequency of administration; and 3) an estimation of the character and prognostic potentialities of the case to be treated.

So far as selection of the drugs is concerned there are at present in clinical use not very many to choose from. Streptomycin, dihydrostreptomycin, para-aminosalicylic acid (popularly known as PAS), and certain of the thiosemicarbazones (of which one only has been used extensively, namely Tibione or T.B., one which is as yet available in this country only for experimental studies). I omit entirely the sulfones (such as promine and promizole) which, though they may have a limited place in the therapy of miliary and meningeal tuberculosis have not been of demonstrated value in pulmonary tuberculosis, either given alone or in combination with streptomycin.

Prior to the development of drug fastness, or more properly stated, the emergence to predominance of resistance, streptomycin and its dihydro derivative are far and away the most effective of these various agents. They are the only ones which exert an unequivocal effect on the course of miliary and meningeal tuberculosis, which is the best clinical standard of reference.[4] The prevailing opinion among those who have used both streptomycin and dihydrostreptomycin is that they are of equal therapeutic activity, although there are isolated reports to the contrary suggesting that dihydro is less effective than regular streptomycin. Dihydrostreptomycin has certainly, on a gram for gram basis, less vestibular toxicity than the parent drug. There have been several reports that the auditory toxicity is greater than that of streptomycin. Our own experience has not confirmed these reports unfavorable to dihydostreptomycin, and we have learned that various other groups have similarly had very little trouble and regard dihydrostreptomycin as having definitely less vestibular and no greater auditory toxicity than regular streptomycin. The conflicting reports may rest on differences in the products of different manufacturers or in the methods of preparation of the solution in the clinic.

The toxicity of PAS appears so far to be inconsequential, except for gastro-intestinal disturbances which make its administration difficult,

especially as it is effective only in relatively large dosage, of the order of 12 grams a day given orally. Tibione, from the reports which Drs. Hinshaw and McDermott brought back from Germany,[5] has sufficient toxic potentialities so that unless and until it is shown that it is more effective therapeutically than PAS, it should be used only in carefully controlled experimental studies. We have ourselves thus far treated only two patients with Tibione and can therefore make no estimate from direct experience of its potential usefulness or of its safety.

As to bacterial resistance, which is well known to be the principal handicap in the use of streptomycin, there have been two recent developments which are encouraging. One is the suggestive evidence in clinical studies by D'Esopo[6] that combining oral administration of PAS with streptomycin therapy delays the emergence of resistance and prolongs the average period of effective streptomycin therapy from approximately two months to a considerably longer period.* The other interesting development is that intermittent therapy with streptomycin alone given every few days, such as twice a week, appears also to delay the emergence of resistance. Whether the total therapeutic effect with such schedules is greater, less or equal to that attained in a shorter time with daily administration of an equivalent total amount has not yet, to my knowledge, been demonstrated. A final consideration concerning resistance is whether the intensity of therapy in terms of the size of the individual dose affects the rate of emergence of resistance. It has been several times stated in the literature that it does not. Tompsett and McDermott,[7] however, in analyzing the bacteriologic data in our series found that intermediate degrees of resistance (in the range between 2 and 100 micrograms per cubic centimeter) appeared more rapidly in the patients who received one gram daily than in those who received 3 grams although the rate of emergence of high degrees of resistance (in the range greater than 100 micrograms per cubic centimeter) apparently had no relation to the dose. Since therapeutic response in the intermediate ranges is at best problematical the inference is that the period of effective therapy is prolonged by the use of the higher dose.

Now combining these various considerations in the first two categories previously referred to, namely that of toxicity and that of

* However, patients receiving PAS have also been found sometimes to have transiently negative sputum or, if positive, a predominance of streptomycin sensitive strains whereas positive cultures with predominantly streptomycin-resistant strains reappear on cessation of therapy. There is a real question, therefore, whether there is not a masking of the resistant cultures rather than a true delay in the emergence of streptomycin resistance by this combined therapy.

bacterial resistance, it appears reasonable to use as large a daily dose of streptomycin as may be possible without undue risk, and to combine this more powerful agent with PAS in order to prolong the action of the former. For the average adult patient a daily dose of 1 gram of regular streptomycin is about as much as can be given without a high incidence of loss of vestibular function. On a weight basis the critical level appears to be 20 mgm. per kilogram of body weight. In our experience, no greater incidence of vestibular or auditory damage has been encountered with 2 grams daily of dihydrostreptomycin, than with 1 gm. of streptomycin. We have used this dosage, namely 2 gm., of dihydrostreptomycin routinely in all adults for more than a year and are continuing with it.

The duration of streptomycin therapy is usually best decided upon in advance and the decision must be based on evaluation of the character of the disease, our third criterion previously stated; and the specific purpose for which the therapy is designed. If to prepare a relatively acute case for collapse therapy, a relatively short course of 4 weeks may suffice. When the first measure of collapse therapy projected is artificial pneumothorax, which is uncertain and may require weeks or months for evaluation before it can be accepted as the definitive treatment, it is best to stop the streptomycin this early in order to partially reserve it for possible future need in connection with surgical measures. When primary thoracoplasty is projected, however, it may be better to continue the streptomycin right on for ninety to 120 days, undertaking the first stage operation as early as may be warranted by the condition of the patient. When a pulmonary resection is planned it may be best to do the operation within the first week of streptomycin therapy and it may be necessary to continue the latter for a total of only three or four weeks. Very often when the need for eventual collapse therapy is apparent, and the disease is not so progressive as to necessitate preliminary streptomycin therapy in preparation, it is best to withhold the drug entirely and reserve it altogether for future eventualities. When the purpose of streptomycin therapy is primarily for treatment of a complication such as tuberculous ulceration in the larynx or of a bronchus, an equally short course of only three or four weeks may be sufficient, but there is some evidence that relapse is less frequent with longer courses. Whenever streptomycin therapy is planned as the sole adjuvant to bed rest in cases which are inappropriate for surgical meas-

ures, courses extending over ninety or 120 days of streptomycin, either daily or interrupted and combined with PAS, seem the most logical. The PAS may be continued for six months or longer. It may develop in the near future that interrupted and combined treatment so consistently delays the emergence of resistance that even minimal tuberculosis may reasonably be treated with streptomycin. In my own opinion this time has not come, and streptomycin should be reserved for the more seriously ill patients. Individualization is manifestly necessary for the best results. I feel sure that Dr. Chamberlain will agree that the consideration of greatest importance is never to give streptomycin therapy until the possible need for eventual surgery is carefully considered. This is essential in order to avoid the premature dissipation of the limited though often critical aid which this agent can render in a coördinated plan of therapeutic management.

A final consideration is whether PAS alone; or Tibione alone; or the combination of these two; may be used in situations in which it is desirable to conserve the resource of streptomycin. No definite recommendation appears to me to be justified at this time, since there is not sufficient evidence regarding, firstly, whether the preliminary administration of PAS may interfere with whatever capacity it has to prolong the therapeutic action of streptomycin when later given in combination, and secondly whether the indubitable anti-tuberculosis activity of PAS, as shown in experimental work, is actually of sufficient potency to be of determinable clinical value when given alone. For the present we are using it freely, both in the aforementioned situations, namely when it is desired to conserve the resource of streptomycin, and in cases of established drug fastness to streptomycin. I personally feel no confidence whatever in my ability to recognize a specific response to PAS in any of the cases which we have treated with this drug alone. The frequent improvements noted in the less severe cases and the occasional improvements in the more severe cases, have all been well within the range of my experience without anti-microbial therapy. A study conducted by a Swedish commission[8] on a chance selection basis is reported to have shown definite therapeutic effects. So far as I know this is the only positive evidence of the clinical value of PAS. About Tibione, I can only quote from the McDermott-Hinshaw report, based on a review of several thousand cases treated in Germany, that this agent "appears to have: anti-tuberculosis activity of the same general order as para-

amino salicylic acid; and a potential toxicity about like the arsenicals used in the treatment of syphilis." This does not recommend it very highly as an alternative drug, in my estimation. Little is yet known about its behavior in respect to bacterial resistance.

As to other anti-microbial agents with experimentally demonstrated activity but in yet earlier stages of clinical evaluation, I know of none which have yet reached even the discussion stage as to their possible practical value.

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CERTAIN ASPECTS OF BENIGN AND MALIGNANT GASTRIC ULCER

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THE purpose of this paper is to discuss the following subjects: first, the role of peptic activity in benign and malignant gastric ulcer; second, the old problem of carcinomatous degeneration of benign ulcer; third, the clinical differentiation of the two lesions; and, finally, the therapeutic implications.

A complete exposition of the role of gastric secretion in peptic ulcer can not be undertaken in this paper. There is abundant evidence[1] to indicate that the process results from the failure of the mucosa to withstand digestion; that the lesion is in fact a "peptic ulcer." The explanation for the failure to withstand digestion is not clear; conceivably, there could be excessive gastric secretion with resultant increase in the attack on the mucosa, or there could be a defective mucosal resistance, or both factors could be operative. In gastric ulcer, however, the quantity of secretion is not excessive; in fact, it is somewhat less than normal, as may be seen from the following table[2] giving the average 12-hour nocturnal fasting secretion in terms of milligrams of free hydrochloric acid:

Normal	661 mg.
Duodenal ulcer	2242 mg.
Gastric ulcer	454 mg.
Gastric cancer	245 mg.

Furthermore, there are some patients in whom the gastric free acidity in response to histamine is persistently low, 20 or 30 clinical units, rather than the usual normal response of 100 to 120 clinical units.[3]

These two facts, (a) that the average fasting secretion in patients with benign gastric ulcer is less than that of normal individuals and (b) that in some patients the secretion is quite low, a true persistent hypo-

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From the Frank Billings Medical Clinic, Department of Medicine, University of Chicago.

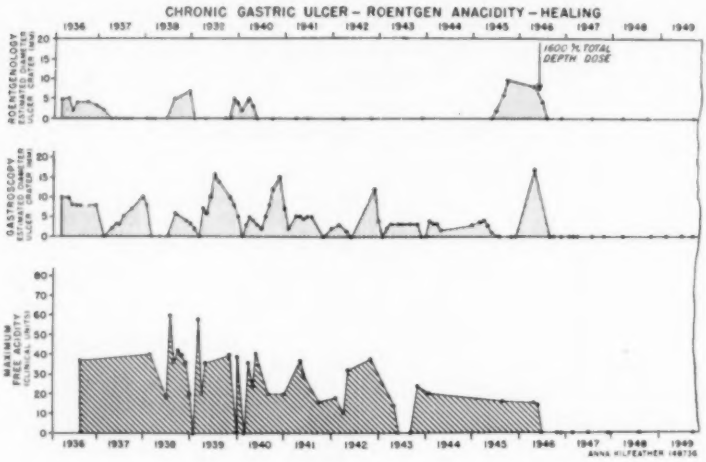

Fig. 1—Course of a chronic gastric ulcer persistently present for 10 years as shown by innumerable gastroscopic examinations; histamine anacidity was induced by roentgen irradiation; healing occurred and has persisted, as has the anacidity, to date (January 1950).

chlorhydria, might be used as an argument that peptic activity plays no role either in the pathogenesis of the ulcer or in its failure to heal. This argument is not valid. The presence of acid (pH of 3.0 or less) can always be demonstrated if one is persistent. A study of 170 cases of gastric ulcer disclosed only 9 in which anacidity was reported after stimulation with histamine hydrochloride; in all of these, the presence of free acid was demonstrated subsequently. Even more convincing evidence of the role of peptic activity is to be found in the fact that whenever a patient with gastric ulcer develops complete achlorhydria, spontaneously or otherwise, the ulcer heals and remains healed for the duration of the achlorhydria. We have been able to produce persistent anacidity in a small group of patients by means of roentgen irradiation of the fundus and body of the stomach.[4] In all of these, the ulcer has healed and remained healed for the duration of the achlorhydria, as illustrated by Fig. 1.

While the role of acid gastric juice seems thus established, it is also evident that the resistance of the mucosa must be decreased; a normal

mucosa should be able to resist digestion, particularly when the acidity is less than normal. The question first asked by John Hunter: "Why does the stomach not digest itself?" comes to us in the reverse form of why is one area digested so easily? It is possible that several factors are involved. Perhaps the protective layer of mucus is accidentally rubbed away; mucus constitutes the first line of resistance to the acid attack. The possible role of vascular and other factors, such as ischemia, has recently received some experimental support in Wangensteen's laboratory.[5, 6] It is quite possible that atrophic mucosal changes may be important. Thus, "atrophic gastritis" was noted gastroscopically in 26 per cent of 150 consecutive patients with gastric ulcer; in 100 patients with duodenal ulcer, on the other hand, the incidence of atrophic change in the mucosa was only 5 per cent.[7] This gastroscopic observation is in accord with the histologic studies of Meyers,[8] Guiss,[9] and Wood et al.[10] It is our impression that the patients with gastric ulcer and the very low-grade secretory rates have an even higher incidence of mucosal atrophy; in fact, it is almost always present. An atrophic mucosa may be abnormally vulnerable to peptic digestion for various reasons, including perhaps a decreased ability to secrete the protective layer of mucus. Some of our most chronic and persistent ulcers have been in this group with very low secretory rates and atrophic mucosae. Complete abolition of the acid, however, does enable the ulcer to heal and insures against recurrence.

In summary, then, benign gastric ulcer results from a rather simple process, the inability of the gastric mucosa to withstand peptic digestion —the so-called acid attack.

In malignant ulceration elsewhere in the body, the necrosis of tissue is usually attributed to inadequate blood supply and to infection. Ulcerations of this type are encountered in the stomach, but they are always recognizable as ulcerating carcinomas. In the acid-secreting stomach a factor is introduced not present in tumors elsewhere, peptic digestion. Neoplastic tissue seems to be less resistant to digestion than is normal tissue. Peptic ulceration may destroy the entire tumor; instances have been described in which multiple sections of the ulcer disclosed no malignancy, yet the lymph nodes contained cancer.[11, 12] As a rule, however, only a portion of the tumor is destroyed. Acid gastric juice and peptic ulceration thus produce in neoplastic tissue a lesion more or less mimicking a benign ulcer morphologically. Mallory[13] has ably sup-

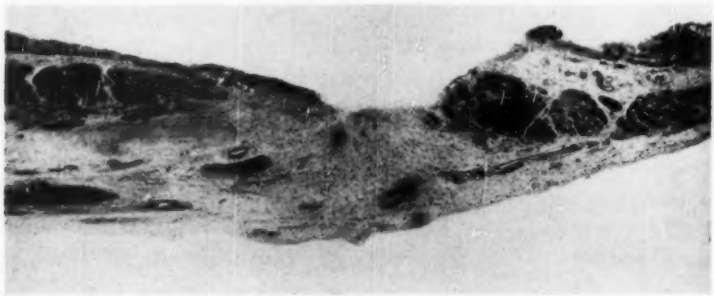

Fig. 2—Peptic ulceration in neoplasm simulating benign ulcer architecturally. Note the complete interruption of the muscular layer with replacement by connective tissue and the fusion of the muscular layer with the m. mucosae at the left side.

ported this view. Fig. 2 is illustrative; the patient died of a rapidly metastasizing carcinoma of the Jarcho[14] type; there was no basis for a diagnosis of pre-existing benign ulcer;[15] architecturally the structure is that of peptic ulceration in neoplastic tissue.

Since peptic digestion plays such an important role in producing the morphologic pattern of benign and malignant ulcer, it is to be expected that the lesions may simulate each other clinically. Every physician knows that this is, indeed, the case. The mechanisms of pain[16, 17] are essentially the same as are those of many of the other clinical manifestations.

According to Goldstein,[18] Cruveilhier[19] in 1829 was the first to differentiate between benign and malignant gastric ulcer and to raise the question of "cancerous diathesis" in chronic ulcer; Rokitansky[20] in 1842 suggested that carcinoma might have its origin in ulcer. In the intervening century, the relationship has been discussed by innumerable pathologists and clinicians. Konjetzny considers chronic gastritis to be the precursor of peptic ulcer[21] and gastric cancer;[22] the continued mucosal regeneration leads to hyperplasia and in time to neoplasia. The histologic evidence of this process as presented by Konjetzny seems excellent. Theoretically, the same sequence of events might take place in the edge of a chronic peptic ulcer; Konjetzny and numerous other workers have taken this view, but the evidence, both pathologic and clinical, is unsatisfactory.

The pathologic criteria of carcinomatous degeneration in benign ulcer, as elaborated by pathologists from Hauser to Stewart, have been reviewed by Bueermann;[23] they consist primarily of the demonstration of the classical features of chronic peptic ulcer; scarring of the muscular wall with fusion of the fibers of m. mucosae and m. propria, an overlying layer of fibrinoid necrosis, and an area of cancer in one edge of the ulcer. Mallory,[13] however, has studied these histologic patterns and reached the conclusion that they are to be interpreted as peptic ulceration of carcinoma in situ. This judgment has been reached by other pathologists as well and seems to me to be entirely valid.

Another argument sometimes offered in support of the theory of carcinomatous transformation is the fact that two different types of carcinoma may be found in opposite edges of an ulcer; this observation is not conclusive for Saphir[24] has shown how different histologically the various areas of a tumor may appear.

The clinical evidence is usually based on patients with a long history of epigastric distress found ultimately to have cancer. This evidence is not of great value, because the distress may not have been ulcer distress and obviously may have had nothing to do with the terminal carcinoma. In some instances a gastric ulcer has been demonstrated followed years later by the finding of a cancer at the same site. Thus, in a case described by Smith and Jordan,[25] a gastric ulcer was shown by x-ray at age 52; the lesion disappeared under treatment; at age 65 when the patient was operated on for gall bladder disease, no evidence of a gastric lesion was found; at age 72, marked mental deterioration developed; at age 75, the patient died of cerebral hemorrhage having had evident gastric symptoms for several months; a carcinoma simplex with mucinous foci was found at the site of the old ulcer although no scar was identified. In cases such as this, there is no proof at all that the ulcer had anything to do with the cancer. Konjetzny,[21, 22] Bueermann,[23] and others have described the simultaneous and independent occurrence of primary gastric neoplasm and benign ulcers or scars. Thus clinical evidence such as this does not prove that malignant degeneration ever occurs.

As yet, no one seems to have observed actually the neoplastic transformation of a benign ulcer. We have followed several patients with frequent gastroscopic and roentgenologic examination for periods as long as fifteen years without noting such a change. Fig. 3 shows the

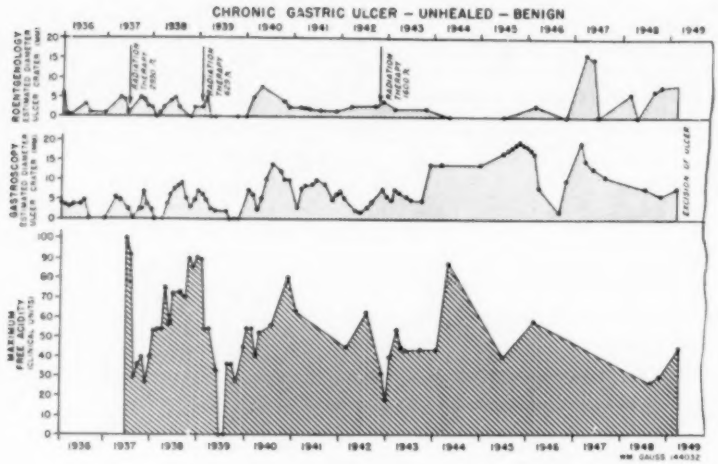
CHRONIC GASTRIC ULCER – UNHEALED – BENIGN
1936 1937 1938 1939 1940 1941 1942 1943 1944 1945 1946 1947 1948 1949
ROENTGENOLOGY
GASTROSCOPY
EXCISION OF ULCER
MAXIMUM FREE ACIDITY
RADIATION THERAPY 4250 R
RADIATION THERAPY 4250 R

Fig. 3—Course of a chronic gastric ulcer followed for 13 years with innumerable roentgenologic and gastroscopic observations; when the lesion was finally resected, it was a perfectly benign ulcer with no evidence of neoplastic transformation.

Fig. 4—"Chronic" gastric cancer. This ulcerating carcinoma was correctly diagnosed gastroscopically and roentgenologically 4 years before its removal surgically; at the time of operation the lesion was small with no evidence of metastases; there has been no indication of recurrent neoplasm in the intervening 7 years.

course of a patient whose ulcer was observed on many occasions during thirteen years; when finally the lesion was excised in 1949, it was still benign. On the other hand, there are some "chronic," slow-growing ulcerating neoplasms which simulate benign ulcer for long periods of time; Fig. 4 is a cross section of one studied at frequent intervals for four years, diagnosed as malignant at the first gastroscopic examination, and yet it was still a small localized carcinoma at the time of operation; there has been no sign of recurrence in the intervening seven years.[26]

In summary, then, it seems fair to state that there is no conclusive proof that neoplastic transformation ever occurs in benign gastric ulcer. The clinical and pathologic evidence thus far adduced can all be explained on the basis of peptic ulceration in neoplasm. On the other hand, the possibility of such transformation has not been disproved; other epithelial lesions, such as varicose ulcers of the skin, do become malignant at times, but analogy does not constitute proof. Until better evidence is available, the possibility of malignant degeneration may be disregarded in routine clinical work. The practical problem confronted by the physician is not that of malignant change in an ulcer, but rather the differentiation, at the time, of the two processes, or more correctly, perhaps, the recognition of cancer in an ulcerating lesion.

There are no diagnostic signs pathognomonic of benignancy; on the other hand, there are certain definite criteria of malignancy. The age, sex, duration of symptoms, severity of symptoms, and type of symptoms are not of great importance for the obvious reason that peptic ulceration can begin in neoplasm at any age and produce the syndrome of peptic ulcer. Massive bleeding may occur; occult bleeding is usually present. Free acidity is to be expected in the benign lesion; its continued absence, using the histamine test, is strong evidence for neoplasm. An ulcer of the greater curvature is almost always malignant. The meniscus sign of Carmen is pathognomonic of neoplasm. There are various other features resulting from the infiltration of the gastric wall with tumor which indicate malignancy. Similarly, on gastroscopic examination the sharply punched-out benign ulcer can usually be distinguished from ulceration in neoplasm by means of the infiltration noted in one or more edges of the ulcer. In some instances, however, this infiltration is minimal and the existence of tumor is not detected. The recent introduction of the cytologic examination of the gastric content affords another method for the detection of cancer in lesions apparently benign.

Conceivably all of these procedures could be employed in a given case with negative results and yet neoplasm be found eventually. In the opinion of many physicians, internists, and surgeons this fact justifies routine gastric resection for all gastric ulcers with the thought that only the microscope is able to exclude cancer completely. However, there are instances in which even the histologic examination has erred; no neoplasm is found and yet the patient returns months later with metastases.

From the standpoint of therapy, the practical question with regard to differential diagnosis is whether benign and malignant ulcer can be differentiated with sufficient accuracy to justify medical management. In arriving at a judgment on this point a number of factors must be borne in mind:

(a) The mortality from subtotal gastric resection for both benign and malignant ulcer is low.

(b) The recurrence rate of benign ulcer on medical management is high, although satisfactory control of the symptoms and of the ulcer is usually achieved.

(c) Recurrent gastric or jejunal ulcer after resection for gastric ulcer is almost unknown.

(d) The prognosis of gastric cancer even with resection is poor—a five-year survival rate of 7 per cent; a certain definite amount of palliation must be added to this figure although it is difficult to estimate in terms of months of life or relief of suffering.

The last point, the poor prognosis of gastric cancer even with modern surgery, should be amplified, for it will be contended that "early diagnosis" would permit surgical cure. Early diagnosis is certainly desirable, the earlier the better, but there is abundant evidence that many gastric tumors, probably the majority, metastasize by the time they produce symptoms or are large enough to be detected by x-ray or gastroscopy. The perfection of a serological test for cancer would probably not identify its location. Hence our ultimate hope must lie either in the prevention of gastric cancer or in a method of therapy which will destroy the metastases as well as the primary growth. The outlook at present is most discouraging. Hence, while "early diagnosis" and complete surgical removal continue to be the only feasible goals, they are, for the great majority of patients, unattainable both now and in the foreseeable future.

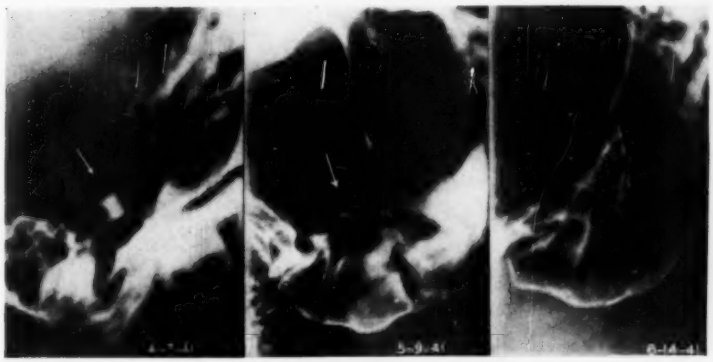

Fig. 5—Healing of peptic ulceration in gastric cancer. Note the disappearance of the crater and the persistence of the infiltration of the gastric wall as indicated by the deformity of the mucosal pattern of the lesser curvature.

It is possible to use this low rate of cure in gastric cancer to support either of two positions: first, that all ulcers should be resected at once in order to remove the cancer as soon as possible; or, second, that very little risk is run by studying a given ulcer for a few weeks before urging its removal in order to be certain that it is malignant. My own procedure is flexible; the decision is based upon an evaluation of the patient, the circumstances and the total evidence, clinical, laboratory, roentgenologic and gastroscopic. There is one point, however, on which it is necessary to be adamant: the benignancy of the ulcer must be proved by repeated roentgenologic and gastroscopic observations; otherwise resection is mandatory. Relief of pain, gain in weight, disappearance of occult blood in the feces, decrease in the size of the roentgenologic niche—all of these may be seen in ulcerating neoplasm.[26] Complete disappearance of the roentgenologic crater may occur; peptic ulceration in cancerous tissue may heal; the regenerated epithelium may consist of normal or neoplastic cells, but neoplasm is present in the wall producing a deformity of the mucosal pattern evident radiologically and gastroscopically. In the instance pictured in Fig. 5, the delay of 2 months in operation cannot be said to have impaired the prognosis, for the patient is still alive and in excellent health more than 8 years after

resection of the cancer. Benign ulcers, on the other hand, should disappear completely and not leave any infiltration of the gastric wall.

In this paper I have endeavored to show that peptic ulceration may develop in a normal mucosa, an atrophic mucosa, or in a neoplasm. The morphology of an ulcerating carcinoma is frequently determined more by the peptic ulceration than by the neoplasm. These are the lesions in which the question of carcinomatous degeneration of a pre-existing ulcer is raised. The existence of such a neoplastic transformation has not been proved; pathologic and clinical evidence both are inadequate; no one has as yet actually witnessed such a process. Peptic ulceration in carcinoma is also responsible for the difficulty in differential diagnosis. The details of differentiation have not been elaborated in this paper; in essence, differentiation consists of the demonstration roentgenologically or gastroscopically of the infiltration of the gastric wall or mucosa so characteristic of tumor, or conversely, demonstration of the complete healing of the ulceration without residual infiltration. The practical diagnostic and therapeutic difficulties may be resolved by the immediate removal of all gastric ulcers—the procedure favored by most surgeons and many internists. Those of us who essay to treat gastric ulcers medically as benign lesions must accept a certain risk, just as the surgeon does in operation. The amount of this risk is a matter of opinion rather than fact. Medical treatment is permissible only if exhaustive study fails to disclose evidence of neoplasm; it may be continued only if the objective methods of x-ray and gastroscopy show healing of the ulcer with no infiltration. The treatment of gastric neoplasm is entirely surgical.

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MODERN GASTRO-DUODENAL SURGERY

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WITHIN the past decade important advances have been made in the care of surgical patients. Among these are:

1. Availability of more blood for transfusions and more liberal use of transfusions before, during and after operation.

2. Control in large measure of distention of the gastro-intestinal tract by means of intubation with the Miller-Abbott or similar tubes.

3. Means for measuring rapidly the sodium and potassium content of plasma and other body fluids with the flame photometer. This, together with tests previously available for chlorides and bicarbonate, permits daily or even hourly supervision of the electrolyte content of the extra-cellular portion of the body. This in turn is a great aid in avoiding edema, an enemy of the surgical patient whose importance is even yet not generally appreciated.

4. The hematocrit and the falling drop method of estimating plasma proteins continue to hold their importance. The former has been supplemented by the T1824 (Evans blue) dye test for blood volume. The accuracy and clinical significance of this test are still being elaborated, but there is no doubt of its use in demonstrating depletion of red cell mass and plasma volume.

5. There is a more general appreciation of the dangers of malnutrition in the surgical patient both before and after operation and means are now at hand for giving fractionated protein and fat by vein and for aiding assimilation of food taken by mouth.

6. Post-operative thrombophlebitis and its sequelae, which can so often be fatal, are usually successfully dealt with by means of dicumarol, heparin and occasionally by ligation of the superficial femoral veins.

7. Atelectasis and the presence of sticky mucus in the bronchial tree are now understood to be sources of danger which must be alertly and

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effectively averted or treated. Post-operative aspiration of the trachea by the anesthetist, frequent turning of the patient after operation, encouraging him to cough, aspiration of his airway, sometimes with the help of the bronchoscope, are simple enough procedures but they were not given enough attention ten years ago.

8. Free use of the antibiotics to minimize infection in the operative field, the lungs, genito-urinary tract or other parts of the body.

9. The clear benefits to the well-being of the patient that derive from getting him mobilized soon after operation.

10. Better understanding by anesthetists of the physiological requirements of their patients during anesthesia.

These advances constitute a very considerable new armamentarium for the surgeon to use and the results are evident in the surgical records. The surgery of the stomach and duodenum has benefited along with the rest until now it is possible to say that major operations for benign lesions of these two organs can be done with an overall post-operative mortality that is small indeed. The relative safety of major procedures for benign lesions of the stomach and duodenum under modern operating conditions is a point to be emphasized, not only because of its bearing upon the freedom of the use of surgery for peptic ulcers, but because it has made possible extensive operations for other conditions that a few years ago would have been impossible to do.

The Safety of Operations for Benign Lesions

This report is based largely on the records of the Presbyterian Hospital for 1948 as a representative example of present day gastro-duodenal surgery. For the decade ending in 1945, it was possible to report from the Presbyterian Hospital a post-operative mortality rate of 4.6 per cent after elective gastric resection for peptic ulcer, with additional deaths after patients left the hospital, resulting from recurrent ulcer or operative errors, that brought the mortality to 6.4 per cent. In contrast, after the same operation during the years 1947, 1948 and 1949 there were no deaths in the hospital and no deaths that we can find record of after the patient left the hospital that can be attributed to the ulcer or the operation. This statement refers to elective resections for benign gastric or duodenal ulcer not complicated by the presence of a previous gastro-enterostomy and not done within a few hours of massive bleeding. During these years over three hundred such resections

TABLE I—OPERATIONS FOR PEPTIC ULCER—1948

Elective resections	114
Emergency resections for hemorrhage	15
Closure of perforated ulcers	15
Posterior gastro-enterostomy	1
Vagectomy with resection	1
Vagectomy with posterior gastro-enterostomy	1
Vagectomy alone	7
Resection for marginal ulcer	3
Excision of gastro-jejuno-colic fistula	2
Miscellaneous	6
Total	165

were done for private and ward patients by many surgeons. The improvement in post-operative mortality and morbidity has coincided with the adoption of the very short loop, post-colic type of anastomosis as a standard technique, a change which supplemented the general advances in surgical care above mentioned.

The accompanying table (Table I) shows the type of surgery that was done for benign ulcer at the Presbyterian Hospital during 1948. It includes all the operations that were done for peptic ulcer in that year.

It is seen that 165 operations were done upon ward and private patients of which 132 (80 per cent) were resections. Only one posterior gastro-enterostomy was done. The patient was a 77 year old man whose symptoms were chiefly those of obstruction. Vagectomy was reserved for patients who had recurrent ulcers following gastric resection (one of whom came from our own clinic) and for a few special situations. In clinics other than ours, groups of patients have been subjected to vagectomy with and without gastro-enterostomy and with extensive or limited resections. It will take many more years to evaluate the results of these procedures. One of the important functions that a national body interested in gastro-enterology could perform would be to provide means for following, in a uniform manner, patients who have undergone the common types of operations in a group of responsible hospitals. Our reason for persisting with resection as our operation of choice is that we prefer the results of that operation to those of any other operation with which we are familiar, and the low post-operative mortality now permits us to offer resection to patients without hesitation

in nearly all cases. Following all the operations listed in Table I there was one death, which occurred as the immediate result of a cerebral accident in a patient who had undergone a gastric resection as an emergency for acute massive hemorrhage. It is not every year that we shall be so fortunate, but the safety factors in operations for peptic ulcer now are high.

Massive Hemorrhage

The matter of how to treat patients with massive hemorrhage from peptic ulcer is still one of controversy. It is hard to give a practical definition of the term "massive hemorrhage" and therein lies one of the main sources of confusion. As one reads medical articles, it is clear that the term means different things to different people. Without attempting a definition, one may suggest that any person who has had active bleeding of such extent that it requires a transfusion of two liters of blood to bring his blood volume and hematocrit back to normal, has had a massive hemorrhage. In the recent literature, recommendations for treating massive bleeding from peptic ulcer range all the way from no surgery at all to resection for all. We have followed a middle course, selecting for operation patients whose response to a non-operative regimen has not been immediately satisfactory. In the eight years ending 1937, among 239 patients who were considered to have suffered a massive hemorrhage from benign ulcer, the mortality was 9.6 per cent. Only six of these patients were operated on as emergencies. The operative mortality was understandably very high, as emergency operations were done only as a last resort. Transfusions were available in those years, but were used sparingly, judged by our present standard, for fear of "blowing off the clot," precipitating new hemorrhage and bringing about a situation where surgery, which was almost synonymous with death, was the only recourse. Here again the present relative safety of gastric resection has changed our policy. The patient who has had a recent severe hemorrhage is not as good an operative risk as one who has not, but the difference is not a governing factor, provided that he can be gotten out of shock for the operation and provided also that the anoxia that attends bleeding and prolonged low grade shock has not so damaged his cells that recovery will be slow or impossible. The mistake that we fear most now is to permit hemorrhage to continue too long, and that is not a matter of time alone but takes into account the rate of bleeding and the general condition of the patient. As a rule, the worse the general

TABLE II—CASES OF SEVERE BLEEDING FROM PEPTIC ULCER—1948.

	Number of Cases	*Number of Deaths*	*Death Rate*
Medical therapy alone	45	0	0
Medical therapy, plus gastric resection, elective	16	0	0
Medical therapy, plus gastric resection, emergent	15	1	6.7%
All cases of severe bleeding	76	1	1.3%

condition of the patient, the less one dares dally with conservative measures if they are not obviously going well.

Table II shows how the cases of massive hemorrhage were treated by the combined team of medical and surgical staff members who attended them as soon as they were admitted. It is an advantage to be able to carry a patient through his hemorrhage by conservative means, even if operation is to be done at an elective time later, for the post-operative course under those circumstances does not present difficulties more than the average. But, of the patients who do not do well from the start on a conservative regimen, more, we are convinced, can be saved by prompt resection than by continuing non-operative measures in the hope that the bleeding will stop of itself. The common dangers following emergency resection for acute hemorrhage do not include death from operative shock if the case has been well managed, but stem from difficulties in properly treating the duodenal stump, secondary hemorrhage from the ulcer if it is not exteriorized from the lumen and thrombophlebitis with its sequelae. Among the seventy-six patients treated for massive hemorrhage in 1948 there was one death, which occurred following a resection. The severity of the bleeding in the cases subjected to operation is illustrated by the fact that they required an average of six liters of blood apiece, some of which, of course, was needed to replace blood lost at operation. It appears that the plan of selecting patients for operation among the massive bleeders is feasible.

GASTRIC ULCERS

Gastric ulcers present special problems. It is claimed that all should be operated on, but gastric ulcers occur that by all tests appear to be benign and that can be demonstrated by repeated roentgen studies to heal rapidly on a conservative regimen and *stay healed* after the patient

has resumed normal activities. It is unnecessary to resect these. Gastric ulcers that recur, even if years intervene between attacks, are another matter and they should be resected.

The chief problem that the surgeon meets treating gastric ulcers, lies in determining their nature. We rely for differential diagnosis between benign and malignant ulcers upon the history, the roentgen ray examination, the acidity of the gastric juice, the location of the ulcer in the stomach, gastroscopic findings, the Papanicolaou stain and the electro-gastrogram. The last is yet in the experimental stage and during 1948 we had not developed at our institution the Papanicolaou method to a practical degree. In half of our cases that proved finally to be benign, one or more of the standard methods of study suggested carcinoma, so that the surgeon went into the operation without a reliable diagnosis. After inspection of the lesion at operation in not a few instances carcinoma still seemed to be the probable diagnosis and unnecessarily extensive operations were done which could have been avoided if it had been possible to know that the ulcer was benign. It must be appreciated that the pathologist with the stomach open before him sometimes cannot tell from gross inspection the nature of a gastric ulcer, that quick frozen section of lymph nodes near the ulcer will not make the diagnosis unless cancer is found and that a simple biopsy of the ulcer itself is unreliable because it may miss the part of the ulcer that contains the carcinoma and because of technical difficulties in getting a good microscopic section of frozen gastric wall. In an attempt to solve this very practical difficulty, a method has been devised for making quick frozen sections of biopsies taken from several parts of the wall and floor of the ulcer after the stomach has been opened at operation and the lesion inspected from the lumen side. It is too early to say that this method has been successful but if it fulfills its early promise it will be possible to treat gastric lesions at operation with much of the precision that we take for granted in treating lesions of the female mammary gland. The importance of this is obvious if one will visualize, for instance, an ulcer high on the lesser curvature with its base on the left lobe of the liver, an ulcer of the posterior wall of the pars media with its base on the body of the pancreas, or an ulcer near the pylorus involving the head of the pancreas. Rational treatment of these ulcers, were they malignant, would be very different from the relatively simple resection that would suffice if they were known to be benign.

TABLE III—GASTRIC NEOPLASMS—PATHOLOGIC DIAGNOSIS—1948

Carcinoma:	
Unclassified carcinoma of the stomach	43
Carcinoma, linitis plastica type	2
Carcinoma, superficial spreading type	1
Carcinoma, colloid type	2
Total Carcinomata	48
Lymphosarcoma	2
Leiomyoma	3
Polyp (i)	4
No pathological diagnosis (inoperable, no spec.)	1

TABLE IV—GASTRIC NEOPLASMS—OPERATIONS—1948

		Deaths
Partial gastrectomy	28	2
Total gastrectomy	7	1
"Compound" resections of the stomach	6	4
Gastro-enterostomy, palliative	7	1
Gastrorraphy	1	0
Gastrostomy (for gastric carcinoma)	3	0
Sleeve resection, palliative	1	0
Excision of polyp (i)	4	0
Esophagogastrectomy, upper one-half	1	0
Esophagojejunostomy, Roux, palliative	1	0
Gastrostomy and gastrorraphy (benign lymphoma, poor risk)	1	0
Excision leiomyoma	1	0
Total	61	8

TUMORS

If this report so far, dealing with benign lesions, has seemed aggressively optimistic, no such attitude will be adopted in discussing gastric neoplasms. One predominately important objective of the surgery of gastric neoplasms has not been realized, namely, a ready method for making early diagnoses in a large proportion of the cases. Instead, the attention of surgeons has been chiefly directed toward diminishing the post-operative death rate and to executing wider and wider excisions of

tissues. The safety factors that we mentioned in relation to the surgery of benign lesions now permit removing at one time, not only the whole stomach, but some or all of the left lobe of the liver, the spleen, the pancreas, the transverse colon with its mesentery, in fact any dispensable organ that is in contact with the growth.

Tables III and IV show the type of neoplasms of the stomach that were surgically treated in 1948 at the Presbyterian Hospital, the operations that were done and the post-operative mortality. About one-third of all the operations were done for palliation alone. The types of tumors that were treated were roughly similar to those of other years. The operations showed a trend toward more extensive surgery. For the carcinomas, for instance, over one-third of the operations that aimed at cure consisted of total gastrectomies or even more drastic procedures in which organs other than the stomach were removed. This trend, to greater or less degree, is common among the larger clinics throughout the country. Will these heroic procedures add substantially to the number of patients that will walk into our follow-up clinics five years after the discovery of their disease? We are yet several years away from the answer.

In planning the surgery of carcinoma of the stomach, one must keep in mind that one is not dealing with an entity. The carcinomas differ among themselves, as if they were a pack of mongrel dogs. We have seen a fungating carcinoma which appeared to have been cut through at operation remain arrested in a patient followed for ten years. At the other extreme, we are all unfortunately familiar with the type of tumor that spreads wildly throughout the stomach and the neighboring lymphatics, impossible now to arrest. We have counted forty-three shallow ulcers in a resected portion of stomach that were apparently all independent foci of carcinoma. It is a disease of many manifestations and the difficulties encountered in treating it surgically are compounded by the fact that the chief routes of lymphatic spread vary with the location of the tumor within the stomach wall. A fungating growth near the pylorus, for instance, would not be expected to spread to the fundus of the stomach but might well metastasize to the lymph nodes of the hepatic chain that lie between the head of the pancreas and the duodenum. To recommend total gastrectomy for all gastric carcinomas seems irrational, especially in the absence of thorough removal of the lymphatics that directly drain the growth. The lymphatic routes are technically

hard to remove, but, with the possibilities of modern surgery, extensive dissections can be done if that is the only way to arrest the disease. We are deterred in planning our surgery by lack of exact knowledge of why and under what circumstances partial gastrectomies have failed in the past. We know that over the years partial gastrectomy has afforded five year arrests to almost half of the patients who survived the operation and whose carcinomas had neither metastasized nor spread to neighboring organs at the time of removal. Unfortunately, these patients are few in number and of the patients who come to even our best clinics with gastric carcinoma only about six or seven per cent are alive five years later. The pressing need now as in the past is the development of a practical method of early diagnosis. Meanwhile, the new benefits that surgery has to offer are, first, increased safety in all operations, including such preventive measures as removal of gastric polyps and recurring or persisting benign gastric ulcer, and, second, the possibility of increasing the arrest rate to some degree by more radical operations.

Summary

Advances made in recent years in the surgery of benign lesions of the stomach have increased the safety of these operations to the point where they may be freely offered to patients who need them. The results following properly selected operations are excellent with few exceptions.

For malignant lesions, in the absence of an established method for increasing the number of early diagnoses, little progress can be reported. The radical operations now being done have not yet had time to prove their worth.

VIRUS INFECTIONS OF THE NERVOUS SYSTEM*

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INTRODUCTION

ALTHOUGH rabies has been known since ancient times, and acute anterior poliomyelitis was recognized as a clinical entity in 1840,[1] our knowledge of the role of viruses in the production of disease of the nervous system is of recent origin. In 1804 Zinke[1] showed that rabies could be produced in a normal dog by the inoculation of saliva from a rabid animal and in 1909 Landsteiner and Popper[2] produced a flaccid paralysis in monkeys by the injection of an emulsion of the spinal cord from a fatal case of poliomyelitis. An ill-defined disease[3] which may have been a form of encephalitis was described under the term of Nona over two centuries ago but it was not until 1930 that a filtrable virus was recovered and definitely proven to be the causal agent of encephalitis in man. The progress of our knowledge of the virus diseases has been rapid in the past fourteen years. The list of viruses which may affect man in epidemic or sporadic forms is extensive and additions to the list are being made each year.

Although the list is extensive, virus infections are not, with the exception of poliomyelitis, a common cause of disease of the nervous system in man. Many of the diseases which will be considered have occurred in the form of localized epidemics or as the result of laboratory infection. The interest in the virus infections has led, however, to their indiscriminate implication in a wide variety of diseases of the nervous system, of unknown etiology. As our knowledge of the viruses increases, some of the diseases of unknown etiology may be proven to be due to them, but advances are retarded by labeling all acute or subacute diseases of the nervous system as virus diseases. Adams and Weinstein[4] have

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TABLE I—VIRUS INFECTIONS WHICH PRIMARILY INVOLVE THE CENTRAL NERVOUS SYSTEM IN MAN. (NEUROTROPIC)

Epidemic Form

1. Acute Anterior Poliomyelitis
2. Equine Encephalitis
   - Western Type (1938)*
   - Eastern Type (1938)
   - Venezuelan Type (1938)
3. Japanese B Encephalitis (1936)
4. Russian Tick-Borne Encephalitis (1937)
5. St. Louis Encephalitis (1933)

* Dates refer to year in which the virus was isolated.

TABLE II—VIRUS INFECTIONS WHICH PRIMARILY INVOLVE THE CENTRAL NERVOUS SYSTEM IN MAN. (NEUROTROPIC)

Non-epidemic Form

1. B Virus of Monkeys (1934)*
2. Louping Ill (1934)
3. Lymphocytic Chorio-Meningitis (1935)
4. Pseudo-Lymphocytic Choriomeningitis (1939)
5. Rabies (1804 and 1935)
6. Swineherd's Disease (1936)

* Dates refer to year in which the virus was isolated.

TABLE III—VIRUS INFECTIONS WHICH SECONDARILY INVADE THE CENTRAL NERVOUS SYSTEM IN MAN. (NON-NEUROTROPIC)

1. Herpes Simplex (1943)*
2. Lymphogranuloma Venereum (1940)
3. Mumps (1934)

* Dates refer to year in which the virus was isolated.

pointed out the fallacy of this kind of logic. They reported that in 15 fatal cases in which the clinical diagnosis of virus encephalitis was made during life, other conditions were the cause of the disease in all 15 cases. These words of caution are not to be taken to mean that the possibility of a virus as the causal agent of a nervous illness of obscure origin should not be considered or that well recognized clinical syndromes of unknown cause should not be studied thoroughly with the techniques applicable to the virus infection.

Classification: Viruses which affect the nervous system have been divided into two groups, neurotropic and non-neurotropic, according to whether or not the nervous system is the primary or secondary site of attack of the disease. This division is not an absolute one and it is difficult to determine in the case of some viruses whether the nervous system is the primary or secondary site of invasion.

The virus diseases of the nervous system are also divided into epidemic and non-epidemic forms. The epidemic form includes poliomyelitis, Western, Eastern and Venezuelan equine, St. Louis, Japanese B and Russian Far East encephalitis (Table I). Von Economo's encephalitis, which occurred in pandemic form, was not proven to be due to a filtrable virus. This disease was first described in 1915 and rapidly spread over the entire world. It has for all practical purposes entirely disappeared, although sporadic cases are occasionally reported. The diagnosis of such cases at the present time is under suspicion because it is made only on clinical grounds.

The non-epidemic forms of virus diseases (Table II) of the nervous system include rabies, lymphocytic choriomeningitis, pseudo-lymphocytic meningitis, Swineherd's disease, louping-ill, and encephalomyocarditis. In addition the nervous system may be occasionally affected by the virus of certain familiar diseases in which the invasion is generally outside of the nervous system. These diseases include (Table III) herpes simplex, lymphogranuloma venereum, mumps, and infectious mononucleosis. The latter disease as well as herpes zoster and von Economo's encephalitis (Table IV) which are primarily diseases of the nervous system, are probably virus diseases although the virus has not been definitely identified in any of these diseases.

Epidemiology: Rabies is transmitted to man and other animals by the bite of infected animals and in rare instances by the bite of the vampire bat, which is capable of carrying the virus without showing any evidence

TABLE IV—DISEASES OF THE CENTRAL NERVOUS SYSTEM WHICH ARE PROBABLY DUE TO A VIRUS. (VIRUS NOT IDENTIFIED)

1. Encephalomyocarditis
2. Herpes Zoster
3. Infectious Mononucleosis
4. Von Economo's Encephalitis

of the disease. Many kinds of lower animals and birds have been implicated as reservoirs of the viruses which produce encephalitis in man. A variety of arthropods have been suspected of serving as vectors for the transmission of these encephalitides, most of which have a seasonal (summer) occurrence. A cycle of transmission has been postulated as being from lower animals to arthropod to man or other higher animals.

The various types of virus encephalitides tend to occur in restricted regions of the world. The uniformity in the size of these various viruses and some degree of serological overlapping has led to the hypothesis that they all have a common ancestor and are modified by such environmental factors as the animal reservoir and the arthropod vector.

Clinical Symptomatology: The symptomatology of poliomyelitis and rabies is well known and does not need any consideration in this discussion. The symptomatology of the majority of the other virus infections of the nervous system are those commonly described by the terms meningitis or encephalitis. These symptoms include headache, stiffness of the neck, irritability, confusion, stupor, coma, convulsions and evidence of focal lesions in the nervous system in the form of hemiplegia, aphasia, paralyses of the cranial nerves and the like. In some of the diseases, for example lymphocytic choriomeningitis, mumps, or infectious mononucleosis, the symptoms are more commonly those of a mild subacute meningitis. In others, particularly the equine encephalitides, signs of focal damage to the nervous system are often in the foreground. It must be understood, however, that there is no constant symptomatology for any form of virus infection of the nervous system that will make it possible to determine from the clinical picture whether the disease is due to a specific virus or even whether it is due to a virus infection or not.

Pathology: The pathological picture of all of the various forms of virus infections of the nervous system has not been fully elucidated. In general the nerve cells are the primary site of the damage when the virus invades the nervous system. Evidence of this invasion may be present in the forms of inclusion bodies within the neurones. With destruction of the nerve cells there is an inflammatory reaction with an outpouring of polymorphonuclear leukocytes and mononuclear cells into the meninges and the perivascular spaces of the parenchyma of the nervous system. Coincidental with the inflammatory reaction there is a proliferation of the microglia. There is considerable variation in the degree, extent and localization of the cellular destruction and inflammatory reaction. With some of the virus infections, particularly in the non-fatal cases of such diseases as lymphocytic choriomeningitis, mumps, and the like, the pathological process is probably limited to an inflammatory reaction in the meninges. In others, for example, the equine encephalitides, the degree of tissue destruction may be so acute that there are small areas of necrosis in the white and gray matter of the brain or spinal cord.

It must be stated, however, that with the exception of the presence of inclusion bodies within the neurones, none of the pathologic findings are specific. In the majority of the fatal cases, it may be difficult to state with any degree of certainty that the changes in the nervous system are the result of a virus infection.

Diagnosis: Since the symptomatology is not specific, it is obvious that the diagnosis of a virus infection can not be established from the clinical picture. The diagnosis[5, 6] of a virus infection and the establishment of the type of the infection must rest upon special diagnostic tests. These tests require laboratory facilities which are not available in most general hospitals. Diagnostic help can be obtained from the local or state health departments or from research laboratories connected with medical schools and research institutes.

The diagnosis can be established in all fatal cases by the injection of suspensions of material from the brain or spinal cord into susceptible animals. Although it is not always possible to establish with certainty the diagnosis of a virus infection in non-fatal cases, infections with the known viruses can usually be identified by one of the following methods (Table V):

1. The injection of blood, cerebrospinal fluid, saliva, nasal washings

TABLE V—LABORATORY DIAGNOSIS IN NON-FATAL CASES WITH VIRUS INFECTIONS OF THE CENTRAL NERVOUS SYSTEM

Diseases	*Virus recoverable from*			*Neutralization test*	*Complement fixation test*	*Non-specific tests*
	Blood	*CSF*	*Other sources*			
Acute anterior poliomyelitis	0	0	Stools, nasal washings	?	0	0
Equine encephalitis—Western	Rarely	Rarely	0	+	+	0
Equine encephalitis—Eastern	Rarely	Rarely	0	+	+	0
Equine encephalitis—Venezuelan	+	Rarely	0	+	+	0
Herpes zoster	0	0	0	0	0	0
Infectious mononucleosis	0	0	0	0	0	Heterophil antigen
Japanese B encephalitis	Rarely	0	0	+	+	0
Lymphocytic choriomeningitis	+	+	0	+	+	0
Lymphogranuloma venereum	Rarely	+	Pus from lesions	+	+	Frei test
Mumps	Rarely	Rarely	Saliva	+	+	Fowl red cell agglutination inhibition
Rabies	0	0	Saliva	0	0	0
St. Louis	Rarely	0	0	+	+	0
Von Economo's encephalitis	0	0	0	0	0	0

or excreta into susceptible animals.

2. The application of complement fixation or neutralization tests.

The first method is applicable only in those cases in which the virus is present in fluids or tissues other than the central nervous system. Viremia or the presence of virus in the cerebrospinal fluid is relatively rare in human infections and is common only in lymphocytic choriomeningitis. The virus of rabies and mumps is present in the saliva and that of poliomyelitis in nasal washings and in the stools of infected individuals.

Complement fixation or neutralization tests are applicable to all of the known virus diseases of the nervous system with the exception of

rabies, poliomyelitis and herpes simplex. In the performance of these tests it is necessary that blood be collected under aseptic precautions. Serum should be removed from the clot as soon as possible, frozen and kept at a low temperature until the tests are made. The diagnosis of a virus infection and the establishment of the type of the virus rests upon the development of antibodies to the infection. It is, therefore, necessary to show that antibodies are not present or are present only in low titer before the acute illness and that they are present in a high titer at a proper interval following the onset of symptoms. Since several to many days are usually required for the development of antibodies, serum removed in the first few days of the illness can serve as the control and serum withdrawn in the convalescent stage, three to six weeks after the onset of the illness, for the determination of whether antibodies have developed.

If antibodies are present in equal titer in both specimens, it can be stated that the acute illness was not due to the virus which is being tested. The positive tests merely indicate that the individual has had at some time in the past an infection with this type of virus.

Non-specific and presumptive diagnostic tests are available for infection with lymphogranuloma venereum (Frei test) and infectious mononucleosis (heterophile antigen).

Treatment: There is no adequate therapy for the majority of the virus infections of the central nervous system. The sulfonamides, aureomycin and chloromycetin are of value in infections with the virus of lymphogranuloma venereum.[6] Preliminary reports also indicate that chloromycetin may be effective in herpes zoster.[7]

Immunization procedures are available for rabies and a few of the encephalitides, particularly the equine group, but immunization against the virus encephalitides has not been given an extensive trial in man and its use has been confined mainly to the protection of laboratory workers. Mass immunization, if it ever became practical, would be a difficult procedure. It would seem, therefore, that the greatest hope for the control of these diseases lies in the elimination of the vectors responsible for their transmission once the latter are adequately known.

Post-Vaccinal and Post-Infectious Encephalomyelitis: Any discussion of the virus diseases of the nervous system is hardly complete without a consideration of the encephalitides and myelitides which develop following vaccination against smallpox and rabies and following

acute infections, particularly the exanthemata. The development of symptoms and signs of involvement of the nervous system following either inoculation of attenuated or killed viruses, or systemic infections with viruses, led naturally to the conclusion that the neurological symptoms were due to invasion of the brain and spinal cord by the virus. The character of the pathological changes in the nervous system in patients who die of post-vaccinal or post-infectious encephalomyelitis is unlike that which is seen in the nervous system of patients with fatal infections with the known viruses. In addition all attempts to isolate a virus from the brain or spinal cord of fatal cases of post-vaccinal or post-infectious encephalomyelitis have yielded negative results. While the pathogenesis of the changes in the nervous system in these cases is as yet unproven, it seems likely from the experiments of Rivers and his associates, and those of Ferraro, Kabat and Wolf[8] and others that they are due to an allergic reaction.

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THE VALUE OF THE BONE PUNCTURE FOR OBTAINING MARROW AS A DIAGNOSTIC PROCEDURE*

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EXAMINATION of the bone marrow used to be an unusual procedure during life. In many instances it was difficult to arrive at a true diagnosis in various types of anemias as well as other medical disorders, and a definite diagnosis could not be established until the bone marrow was examined at postmortem. Such patients were seen without a clear diagnosis not only during a short sojourn at the hospital, but during many years of observation.

Very little attention was paid to the suggestions of two Italian observers, namely Pianese in 1905[1] and Ghedini in 1908,[2] that marrow could be obtained during life, by trephining the femur or by the insertion of a stout trocar and canula into the tibia. In our experience, this procedure proved to be almost a major operation. This limited the number of cases in which it could advantageously be performed.

A more practical method was the trepanation of the sternum, as reported by Seyfarth in 1923.[3] This surgical procedure could be performed under local anesthesia. By this means not only could good smears be obtained from the marrow which had been scooped out from the marrow cavity, but also sections could be made for the study of the structure and the distribution of the cells such as hypoplasia or hyperplasia or their replacement by fat or fibrous tissue. A disadvantage of this method was the resulting scar over the sternum which was especially resented by female patients. Another drawback was the difficulty of repeating the biopsy and the limited number of cases that could be subjected to this procedure.

The Bone Puncture: The report of Arinkin in 1927[4] that marrow could be obtained from the sternum by means of a spinal puncture

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needle has led to a great enthusiasm for the study of the bone marrow. This procedure has many advantages:

1. It is simple.

2. It can be performed in an almost painless manner by the use of novocaine.

3. It can be used in infants and children as well as adults.

4. Repeated punctures can be performed to follow the serial changes in the bone marrow under certain conditions as reported recently in pernicious anemia by Erf and Wimer,[5] following B-12 or in multiple myeloma treated with stilbamidine by Snapper and his co-workers[6] and with urethane by Loge and Rundles.[7]

Bone marrow can be obtained in almost all cases except those in which there is an increased density of the bone (osteopetrosis), or in cases of replacement of the bone marrow by fatty, fibrous tissue or cancerous metastases. Only in this small percentage of cases is a biopsy of the sternum or of the ilium indicated.

This simple method of extracting marrow for careful study and evaluation has gained widespread use. While visiting other hospitals, I have lately been very much impressed with the increased frequency with which this procedure is employed. Since the publications from our own Hematology Laboratory by Vogel, Erf, Bassen and the author since 1937,[8-10] over 6000 additional sternal, crest or spinous process punctures were performed. Furthermore, it is noted that the communications on this subject have increased from year to year. Most of the work on this subject has been collected recently and has been well summarized, particularly in the monographs of Rohr[11] and Leitner,[12] as well as in the shorter monographs by Reich[13] and Israels.[14] These writings indicate that the bone puncture is achieving considerable importance in the study of blood diseases, especially leukemia, anemia, leukopenic states and disorders involving the blood platelets, as well as certain metabolic diseases and skeletal metastases. The results of the study of the marrow are extremely valuable for the establishment or confirmation of the underlying medical diagnosis.

Are There Any Dangers Connected With Bone Puncture? Judging from the large numbers of bone punctures performed since 1929, only a few isolated accidents have occurred. In the unusually large series of our own puncture, such as the sternum, the ilium and the spinous process, only one death has occurred. This resulted from a cardiac puncture. This

patient had already had several punctures in which, as a result of myelofibrosis, marrow could not be obtained. In only one case did a complication ensue from puncture of the spinous process, namely a partial paraplegia. This resulted from a softening of the body of the vertebra by an abscess. Only a few mishaps have been reported. Two deaths from sternal puncture have been reported by Breitenecker[15] and one each by Alder[16] and Hadorn.[17] Meyer and Halpern[18] reported a death as a result of shock and fear.

As a rule, it appears to be difficult to pierce the posterior plate of the sternum. One usually feels a "give" upon entering the marrow cavity, so that with proper precautions and increasing experience the sternal puncture can be considered a safe method.

Site of the Puncture: The term "bone puncture" is used with reference to the puncture of any bone of the skeleton for the purpose of obtaining marrow. Its cellularity varies in different bones, but the differential count is relatively unchanged, according to Nordenson.[19]

The three main areas of preference are:

1. The first, second, third bone of the sternum or manubrium.

The manubrium is preferable in infants and children as it is more cellular and accidents are less likely to occur if the posterior plate is punctured.

2. The spinous process. The use of this bone was suggested by Heidenreich and Heidenreich,[20] as well as by Loge[21] as recommended by Japanese investigators and Bickel and della Santa.[22]

3. The iliac crest. This area has been used by Nordenson,[19] van den Berghe and Blitstein.[23] In a recent report, Rubinstein[24] indicated that the iliac crest is preferable in suspected cases of multiple myeloma or skeletal metastases.

The spinous process is a good bone to use in most instances, particularly with apprehensive individuals, since the patient cannot see the procedure. The sternum should be used, if the spinous process or the crest does not yield adequate marrow.

Amount to be aspirated: The site of the puncture should be painted with iodine or some other antiseptic. The skin and periosteum should then be anesthetized with one or two per cent procaine. After a five minute wait, the needle should be inserted with a firm rotatory motion until it penetrates the bone and gives sensation of yielding. Recently we have used two syringes in the aspiration of the bone marrow. With a 20

TABLE I—DIFFERENTIAL COUNT OF NORMAL BONE MARROW

		Per Cent
Myeloblasts	—	0 — 3
Progranulocytes	—	0 — 4
Myelocytes		
Neutrophilic	—	10 — 30
Eosinophilic	—	0 — 4
Basophilic	—	0 — 1
Metamyelocytes	—	3 — 10
Band cells	—	10 — 30
Segmented		
Neutrophilic	—	10 — 30
Eosinophilic	—	0 — 4
Basophilic	—	0 — 0
Plasmacytes	—	0 — 3
Lymphocytes	—	1 — 15
Hematogones	—	0 — 10
Rubriblasts (Megaloblasts)	—	0 — 0
Prorubricytes	—	0 — 1
Rubricytes (Erythroblasts)	—	2 — 15
Metarubricytes (Normoblasts)	—	7 — 30
Average Nucleated Cells	—	100,000
Megakaryocytes	—	44

cc. syringe, we usually draw up a slight amount of blood and marrow, sufficient to cover the lower plate of the syringe. This amounts to about 0.2 cc. and is used for direct smears and a count of the nucleated cells and megakaryocytes. These smears, especially bone marrow particles, are more important for cellularity and the differential count (Table I). Immediately afterwards, with another syringe, 1 cc. of the marrow is aspirated through the same needle and injected into a small test tube containing heparin or oxalate. Some prefer the latter method, especially Reich,[13] Limarzi,[25] and the Mayo group. This method has led to the finding in the buffy coat of the characteristic cells in lupus erythematosus by Hargraves et al.[26] and in the peripheral blood by Sundberg and Lick.[27]

Microscopy of the Bone Marrow: The smears of the marrow correspond with the cell counts and present three types of cellularity, namely:

1. Hypocellular with low cell counts (5,000 to 25,000).
2. Normal cellularity (25,000 to 150,000 nucleated cells).
3. Hypercellular (150,000 to over 500,000) is normal for children.

The three main series of cells according to their frequency are the granulocytes, nucleated red cells and megakaryocytes both immature and mature. In addition, lymphocytes, hematogones and reticulum cells are present in smaller numbers. They vary considerably in the differential count as illustrated in Table I. Marked radical changes in the cellularity, in replacement or hyperplasia of certain cells are therefore important for diagnostic purposes. Attention is called to the new and improved nomenclature of the various cells in the table, especially of nucleated red cell series.[28]

Marrow Changes Occurring In Various Diseases

In a general survey of the unusually large number of bone punctures from the sternum, spinous process or iliac crest, it was found that in a restricted number of instances this procedure was of prime diagnostic importance. In others it was of confirmatory value, and in still others was chiefly of value in excluding certain suspected conditions.

A. puncture of diagnostic importance

The bone marrow proved to be diagnostic in some cases in which the peripheral blood and sometimes the clinical studies were not suggestive of any specific conditions. The most important were the following:

1. Metabolic disorders in which the bone marrow appeared relatively normal, but scattered in the smears were prominent large reticulum cells showing various types of stored lipoids.

a. In Gaucher's disease reticulum cells were characterized by the presence of needle-like kerasin crystals which rendered a reticulated appearance to the cell. In a few cases of Gaucher's disease it was possible to make this diagnosis although splenomegaly was not present.

b. Hand-Schiller-Christian's disease—the crest of the ilium is the bone of choice for finding the reticulum cells showing a diffuse vacuolization of cholesterol material.

c. Niemann-Pick's disease showed foam-like cells which contained a phosphatid substance.

II. *Protozoal Infections.* a. Kala-azar—the bone marrow shows the presence of non-lipoid reticulum cells, some of which are filled with Leishman-Donovan bodies.

b. Histoplasmosis.[29] Increase of reticulum cells showing phagocytosed histoplasma organisms.

III. *Hyperplasia of marrow cells.* The bone marrow also proves diagnostic in some cases in which the blood does not show specific changes, but the normal cells of the bone marrow are apparently displaced by a more or less marked increase of immature or abnormal cells.

a. Multiple myelomatosis. Although the diagnosis can be indicated by the presence of anemia, rouleaux formation of the red cells, hyperglobulinemia, positive formol-gel test and Bence-Jones protein in the urine, some of these changes may be absent or overlooked. An increase of plasma cells, varying from 3 to 90 per cent, definitely establishes the presence of myeloma. Multiple myelomatosis may occasionally be associated with hemolytic anemia and polycythemia, as reported recently by Lawrence and Rosenthal.[30]

b. Aleukemic leukemia. The blood picture of this form of leukemia may not show the presence of sufficient characteristic increase of immature cells in the blood. The diagnosis may be suspected by the presence of lymphocytosis, thrombocytopenia as well as lymphadenopathy or splenomegaly. A similar picture is so frequently found in other conditions (Table II) that the diagnosis can only be made with absolute certainty by the finding of a marked increase of immature cells, myeloblasts or promyelocytes or lymphoblasts in the marrow. These immature cells may appear later in the blood during the progress of the disease.

c. Follicular lymphoblastoma. The presence of a marked increase of hematogones in the marrow as well as in the blood is highly suggestive of this disease. At first sight the blood and bone marrow may resemble lymphatic leukemia. The hematogones resemble lymphocytes but have more compact and darker staining outlines, often with indented nucleus and practically no cytoplasm.[31]

IV. *Skeletal metastases.* There are some instances in which the condition may not be suspected, since the clinical picture may resemble various types of anemia, especially of the osteosclerotic type of a hemorrhagic disease. Certain x-ray findings in the bones may suggest this condition. A sternal or crest puncture may reveal either a scattered or diffuse involvement with clumps of neoplastic cells.

B. Bone Puncture of Confirmatory Value

The diagnosis of most diseases of the blood can be made by means of the history, clinical studies and especially the blood picture. The bone puncture is not the main diagnostic procedure but is helpful in confirm-

TABLE II—VARIATIONS OF THE MARROW IN LEUKOPENIC AND LYMPHOCYTIC STATES

Patient	*RBC* × 10^6	*WBC* 10^3	*Myelo-blasts*	*Myelo-cytes*	*Polynuc-lears*	*Lympho-cytes*	*Mono-cytes*	*Bone Marrow*
1.	2.95	3.2	0	3	25	71	0	Myeloblastic leukemia
2.	3.15	5.2	0	0	11	88	1	Lymphocytic leukemia
3.	4.98	5.9	0	1	53	38	5	Lymphocytic leukemia
4.	3.86	6.0	3	5	13	71	5	Progranulocytic leukemia
5.	2.38	5.3	0	1	35	53	8	Multiple myeloma
6.	5.89	3.4	0	0	45	44	10	Normal (Hypothyroid)
7.	2.94	2.1	0	0	0	94	6	Hypoplastic (Agranulocytosis)
8.	1.6	1.85	10	18	14	48	0	Aplastic (Myelofibrosis)
9.	5.4	1.0	0	0	0	69	31	Progranulocytic (Agranulocytosis)

ing the diagnosis or for repeated examinations in order to show the trend or the underlying condition. Most important of these are the following:

I. *Disorders of the leukocytic elements*, especially leukemia. From previous studies it appears that the myeloid type arises from cells in the bone marrow and may involve the lymph nodes and spleen. The cells in the marrow are most frequently the immature granulocytic elements—myeloblasts, progranulocytes, myelocytes and occasionally the plasma cells, reticulum cells and hematogones.

The second main group of leukemia arises from the lymphocytic and lymphoblastic cells in the lymphatic nodes and spleen, and usually involves the bone marrow by hyperplasia or infiltration. It is also possible that, in a few cases of lymphatic leukemia, the bone marrow may be the main center of involvement, appearing without lymphadenopathy (medullary lymphatic leukemia) or, occasionally, with only splenomegaly. It is possible that the bone marrow may not be involved at first but may become generalized at a later period.

The marrow is of greatest interest in the leukopenic states. Table II illustrates the unusually large number of blood disorders, splenic diseases

and other metabolic conditions which may show marked resemblance in the blood picture. These may show other variations, such as anemia, purpura, hepatosplenomegaly or lymphadenopathy which tend to indicate the possible underlying condition. However, the bone marrow is the most decisive factor for the differential diagnosis of leukemia, hypersplenism, Gaucher's disease, agranulocytosis (maturation arrest), hypothyroidism, constitutional or cyclic leukopenia.

II. *The anemias.* The four main groups of anemias differ very widely in the bone marrow findings. Most important are the following:

a. Macrocytic anemias, such as pernicious anemia or sprue, showing the characteristic rubriblastic (megaloblastic) marrow and showing also a tendency toward marked immaturity of the nucleated red cells.

b. Various forms of hypochromic anemia due to blood loss, neoplastic conditions, nephritis, thyroid dysfunction, either show a normal bone marrow or an increase in the rubricytes and metarubricytes (normoblasts).

c. Hemolytic anemia. The marrow usually shows marked increase of rubricytes and metarubricytes (erythroblasts and normoblasts). The aplastic phase in this condition, as reported by Owren,[32] is rare.

d. Aplastic anemia. The bone marrow consists of three types:

1. Total aplasia of the marrow including the granulocytic and megakaryocytic cells and nucleated red cell elements. The bone puncture reveals fatty and hypocellular marrow.

2. Congenital aregenerative anemia or hypoplastic anemia. The bone marrow is found to be normal except for an almost complete absence of nucleated red cells.[8]

3. Osteosclerotic anemia. The bone puncture reveals a hypoplastic marrow but the blood picture is leukemoid. This disease may be considered as a form of leukopenic myelocytic leukemia. It is also found in the late or spent phase in some cases of polycythemia. It is in these conditions that trepanation of the sternum or ilium is necessary for confirmation of this condition.

III. *Thrombocytopenia and thrombocythemia.* The marrow is of some importance in differentiating the various types of idiopathic purpura. There are three main types of myelograms according to the recent investigations in this field by Leitner,[12] Dameshek and Miller,[33] Diggs and Hewlett.[34]

a. Megakaryophthisis. Absence of giant cells in marrow is rare.

b. Variation in number of megakaryocytes from normal to very high values occurs in the main forms of chronic idiopathic purpura. In addition, there are variations in the maturation of the nuclei and cytoplasm. In general, there is a marked decrease in platelet formation from the megakaryocytes, which is corrected following splenectomy.

c. A normal megakaryocytic picture may be found in some cases of purpura accompanied often by anemia, leukopenia and splenomegaly—thrombolytic purpura—or in hypersplenism.

C. Bone Puncture for Exclusion of a Blood Condition

A majority of the punctures fall into this group. They reveal normal findings which frequently permits one to rule out a suspected hematologic condition.

This is of particular importance in certain infectious conditions such as, sepsis, infectious mononucleosis and monocytosis. The marrow is frequently examined in various leukopenic states, such as constitutional, cyclic or accompanying infections, hypothyroidism and hyperthyroidism, as well as various types of anemia to exclude some form of blood dyscrasia. It is also indicated in various types of bleeding in order to exclude an underlying cryptogenic leukemia or a genuine hemorrhagic diathesis.

In general the study of the bone marrow has now become of considerable importance not only as a diagnostic procedure as outlined above, but as an integral part of the routine procedure for a complete investigation of the patient.

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SECTION ON MICROBIOLOGY

WEDNESDAY EVENING, MARCH 15, AT 8:30 O'CLOCK

I. EXECUTIVE SESSION
   a. Reading of the Minutes
   b. Recommendations of Nominating Committee
   c. Nomination of Section Officers and One Member of Advisory Committee

II. PAPERS OF THE EVENING
   a. Antihistaminic agents — studies of their metabolism by means of quantitative analytical methods
      Ely Perlman
      The Mount Sinai Hospital
   b. A mutation to heat resistance in a bacterial virus
      Mark H. Adams (by invitation)
      New York University College of Medicine
   c. Further experiments with Col. SK virus
      Claus W. Jungeblut
      Columbia University College of Physicians and Surgeons
   d. Modification of the course of a viral pneumonia in mice
      Harold S. Ginsberg (by invitation), The Rockefeller Institute for Medical Research

FRANK L. HORSFALL, JR.
Chairman
The Rockefeller Intitute for Medical Research

HARRY MOST
Secretary
New York University
College of Medicine

Antihistaminic Agents—Studies of Their Metabolism by Means of Quantitative Analytical Methods

ELY PERLMAN
The Mount Sinai Hospital, New York

Hundreds of antihistaminic compounds have been synthesized since the initial studies of Bovet and Staub and some two dozen are available for clinical use. Until recently, studies of their metabolism have been restricted because the sensitive pharmacological assay methods are not applicable. Gelvin, McGavock and Drekter studied the absorption and excretion of Benadryl and Pyribenzamine by means of the Brodie and Udenfriend test for organic bases, and more recently Fleming and Rieveschl have synthesized Benadryl containing radioactive carbon. Studies with this labelled antihistaminic were reported by Dill and Glazko and were briefly described.

A fluorometric method suitable for the determination of a number of available antihistaminic compounds was described. The addition of cyanogen bromide to these compounds results in a new substance which exhibits an intense blue fluorescence when exposed to ultraviolet light. It was found that fluorescence develops only with those

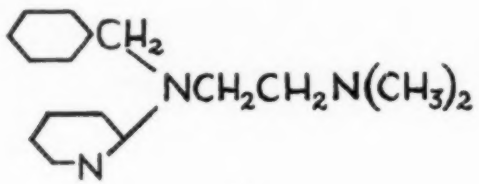

Fig. 1

antihistaminic substances which contain the three nitrogen atoms in the same configuration as found in Pyribenzamine (Fig. 1).

Those antihistaminics which contain the pyridine radical only, develop a color which can be intensified with coupling agents such as p-aminoacetophenone.

The test was applied to a study of the urinary excretion of Pyribenzamine from patients receiving this medication. No free bases were obtained when such urines were made alkaline and extracted with organic solvents. It was found, however, that if such urines were heated with alkali, material could then be extracted with organic solvents which would develop a fluorescence with cyanogen bromide. This material appears to be Pyribenzamine in view of the fact that it could be precipitated as the picrate with the same melting point as Pyribenzamine picrate, and mixed crystals exhibited the same melting point. It was further shown that the isolated material had antihistaminic activity by pharmacological test. The material was also studied at three values of pH in the Beckman ultraviolet spectrophotometer and was found to have identical maxima, minima and isobestic points as found for Pyribenzamine itself.

Applying this method to a study of the rate of excretion of single doses of Pyribenzamine in patients' urine, it was found that about 10 per cent of the ingested dose was excreted in 24 hours and that intravenously administered Pyribenzamine was excreted at the same rate and to the same extent as the same dose taken orally.

*A Heat Resistant Mutant of Bacterial Virus T5**

MARK H. ADAMS

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Bacteriophage T5 is a bacterial virus capable of infecting and lysing strain B of E. coli. In a previous paper,[1] I described a peculiar instability of phage T5 when diluted in saline. This virus in broth is quite stable being rapidly inactivated only at temperatures above 70°C. However, when diluted in 0.1 N NaCl the virus is as rapidly inactivated at 30°C as it is at 70°C in broth. The addition of 10^{-2} M concentrations of divalent cations such as Ca++ and Mg++ to a 0.1 N NaCl solution gave a diluent in which the virus was as stable as in broth.

The addition of small amounts of these divalent cations apparently stabilized the virus against inactivation by heat. Equivalent concentrations of citrate ion would

* Aided by a grant from the National Foundation for Infantile Paralysis, Inc.

prevent the protective effect of calcium and magnesium indicating that the metal ions were responsible for the protective effect since the un-ionized metal-citrate complexes did not protect the virus. A similar protective effect could be demonstrated with sodium and potassium ions but only at relatively high concentrations of the order of one molar, and this protective effect was not reversed by citrate ions.

The kinetics of temperature inactivation of the virus were those of a first order reaction until at least 99.9 per cent of the virus was inactivated. Last summer we commenced a more quantitative study of the interaction between virus T5 and cations using a freshly prepared stock of virus, and to our surprise the results were somewhat different from those we had observed at first. In these experiments, the virus preparation was suitably diluted in 0.4 N NaCl and heated at 50°C, samples being withdrawn at intervals for assay of the surviving viable virus particles.

If for instance we start with 50,000 virus particles per sample, after 5 minutes heating, the virus is 90 per cent inactivated the count being 5,000 per sample. The rate of inactivation then becomes progressively slower until after 30 minutes there are about 700 survivors that withstand heating for as long as 6½ hours. The proportion of heat resistant survivors is a constant, about 2 per cent, regardless of the total number of virus particles with which one starts. It is evident from these results that the virus stock was not homogeneous with respect to stability to heat in 0.4 N NaCl diluent. About 98 per cent of the virus particles were inactivated in the first 30 minutes, but the remaining 2 per cent seemed to be stable indefinitely at 50°C.

An obvious question concerns the nature of the stability of this remnant of the population. Are these particles stable because they have undergone some genetic modification or is there some other explanation? A simple test is to subculture the surviving virus particles and see whether the heat resistance is an hereditary property or not. The surviving virus particles were plated with the host cell on an agar plate to give about 100 plaques. A single plaque was stabbed with a sterile needle and this was used to inoculate a growing culture of E. coli to produce a new stock of T5 phage, descended from a single heat resistant virus particle. When this new stock of virus was heated in 0.4 N NaCl at 50°C, it was stable, hence the property of heat resistance appears to be hereditary. The heat resistant virus has been subcultured repeatedly without loss of this characteristic.

Similarly if a single plaque from the original unheated stock is picked and used to produce a new stock, this stock is found to be composed of at least 99.9 per cent of the heat susceptible form, rapidly inactivated at 50°C; so that we have two stocks differing in their resistance to inactivation by heat. Both heat susceptibility and heat resistance are passed in hereditary fashion in subcultures of these stocks.

These two stocks of phage T5 were similar in all the properties tested except for their susceptibility to heat inactivation in saline solutions.

1. They are inactivated at the same rate by anti T5 serum.
2. They adsorb to their host cell at the same rate.
3. The latent period of intracellular growth and the burst sizes of the two stocks are the same.
4. Both stocks fail to multiply in the host cell unless calcium ion is present in the medium, and both strains require the same amount of calcium ion for optimal growth.
5. Neither stock is able to lyse the bacterial mutant B/1,5 which is resistant to ordinary wild type stocks of phage T5.

Apparently the heat resistant variant of phage T5 has arisen as a mutation, and so far we have found no other difference between the two stocks which might be correlated with the increased heat resistance.

We may now turn to the quantitative aspects of the heat stability of the two forms of phage T5. When heated in broth at 70°C or above, both forms of phage T5 seem to be inactivated at exactly the same rate. That is, they are equally stable in broth. However, in 0.1 N NaCl, the heat susceptible variety is rapidly inactivated

at 30°C, whereas the heat stable variant must be heated to 50°C before inactivation proceeds as rapidly. As the sodium ion concentration is increased above 0.1 N the stability of the variant of phage T5 increases until at about 0.7 N sodium ion the virus must be heated above 70°C and is as stable as in broth. If the log of velocity constant for inactivation is plotted against the reciprocal of the absolute temperature, the points for any single sodium ion concentration tend to fall along a straight line. This is a general finding in kinetic studies, and these curves particularly with respect to their temperature ranges and their slopes resemble curves obtained in heat denaturation of proteins, so presumably the inactivation of T5 virus by heat is the result of protein denaturation. It is not possible to study the inactivation of phage T5 at 50°C at all concentrations of sodium ion since at higher concentrations the inactivation is too slow. However, the curves may be readily extrapolated to intersection with the 50°C ordinate enabling one to calculate what the velocity would be at 50°C and any sodium ion concentration. By this means it is possible to compare the heat susceptible ancestor with its heat resistant mutant with respect to stability at 50°C in various concentrations of sodium ion. At low concentrations of sodium ion the ancestral type is inactivated nearly 10,000 fold more rapidly than is its mutant. As the sodium ion concentration is increased the stability of both forms of phage T5 increases until at about 1 N sodium ion both stocks reach the same upper limit of maximum stability. This upper limit is the same as the stability found in broth or observed on the addition of optimal amounts of calcium or magnesium ion. Apparently the essential difference between the heat resistant mutant and its heat susceptible ancestor is an enormous difference in resistance to heat denaturation in solutions of low ionic strength.

Now let us turn to the heat susceptible form of phage T5. Single plaque stocks of this variety are rapidly inactiviated at 30°C in 0.1 N NaCl to the extent of 99.9 per cent. The remaining 0.1 per cent of the virus particles in these stocks are relatively heat resistant. In a series of single plaque stocks this figure of 0.1 per cent of resistant survivors has been remarkably constant. At first it was thought that these resistant survivors represented the progeny of new mutations to heat resistance. However, when these resistant survivors were subcultured and tested they were found to be genetically heat susceptible rather than heat resistant. It would appear then that there are at least three kinds of T5 phage particles with the following distinguishing characteristics:

1. Phenotypically and genotypically heat susceptible.
2. Phenotypically and genotypically heat resistant.
3. Phenotypically heat resistant but genotypically heat susceptible.

This third class occurs to the extent of 0.1 per cent of the population in stocks of the first class.

Stocks of the third variety can be readily prepared by heating stocks of the first class under conditions in which all phenotypically heat susceptible forms are destroyed. The properties of these heat resistant survivors appear to be the same as the properties of the heat resistant mutant *except* that the property of heat resistance is not transmitted to their offspring.

The mutant is of interest as a tool in the study of virus genetics, since at present there are relatively few genetic markers for viruses known. A few experiments have already been carried out along these lines. For instance, the mutation rate from the heat susceptible to heat resistant form is of the order of one mutation in every 10^6 duplications of the virus. Also it has been found that single bacterial cells can be infected with both resistant and susceptible forms of virus T5, and such cells will on lysis liberate both forms indicating no interference phenomenon with this particular pair of viruses.

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Modification of the Course of a Viral Pneumonia in Mice

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That viral multiplication can be inhibited after infection is established has been demonstrated.[1, 2] Indeed, such inhibition of multiplication of certain small viruses, pneumonia virus of mice[1] and mumps,[2] can be accomplished with type specific capsular polysaccharides of Friedländer bacilli as long as 4 days after the initiation of infection. The experimental data clearly indicate that the carbohydrate neither acts directly on the virus to cause inactivation by combination or by a direct viricidal effect, nor does it prevent the initial step in viral infection, namely, host cell-virus combination.[1, 3] That the polysaccharide does not hinder the liberation of newly formed viral particles from parasitized cells has also been shown.[4]

The available experimental data suggest the hypothesis that capsular polysaccharide of Friedländer bacillus inhibits multiplication of mumps virus and pneumonia virus of mice by combining with or competing for some host cell constituent which is present in susceptible cells in limited quantity, and is not necessary to maintain life of the host cells, but is required by the virus for multiplication.

The postulate raises this question: Can the polysaccharide actually alter the course of a viral disease after infection is well established? It is the purpose of this paper to report experiments in which the capsular polysaccharide of type B Friedländer bacillus, Fr.B, was employed to modify the course of disease caused by pneumonia virus of mice, hereafter referred to as PVM.

PVM, a latent agent of mice, can induce fatal pneumonia in its natural host,[5] and thus the disease which is associated with extensive viral pneumonia appeared an ideal model for the present study. In addition, the qualitative and quantitative aspects of the pathogenesis of this respiratory disease have been carefully and extensively studied.[6]

The experiments were carried out as follows: Mice were inoculated intranasally with 100 M.S.50 doses of virus, a quantity sufficient to cause early disease which is fatal in 5 to 7 days. Series of mice were given a single injection of Fr.B intranasally, 20 ug. per mouse, either 2 or 3 days following the initiation of infection. Control series of mice received saline intranasally at the same times. Groups of 6 mice in each series were killed at 2-day intervals commencing 4 days after viral inoculation. The degree of pulmonary consolidation was scored, and the concentration of virus in the lungs determined by hemagglutination titrations.[7]

All control animals were dead by the seventh day, and the lungs of the mice which succumbed to the viral infection were completely consolidated. On the other hand, almost all mice which received polysaccharide 2 days after viral infection was initiated survived the entire experimental period, showed a maximum pulmonary consolidation of only about 40 per cent of the lung, and had a progressive resolution of the pneumonic process. The mice which were injected with a single dose of polysaccharide, 20 ug. per mouse, 3 days following the inoculation of PVM had more extensive pulmonary consolidation, about 55 per cent of the lung, than did those treated a day earlier in the disease, and in each group 1 to 3 mice died. However, these mice showed a marked reduction in the extent of the viral pneumonia as compared with the control mice, and despite the extent to which viral multiplication and pneumonia had progressed in these animals treated late in the course of the disease, the majority survived the entire experimental period. At this time their lungs revealed no pulmonary consolidation, and no virus could be demonstrated in them.

A comparison of pulmonary lesions and viral concentration in mouse lungs reveals that the increase in viral concentration pre-

ceedes the development of pneumonia. In the control series the greatest concentration of PVM, 1:512, was reached after 6 days, whereas maximum consolidation, 100 per cent, was present 7 days after the initiation of infection. Following the intranasal injection of Fr.B, 2 or 3 days after the initiation of infection, there was no further increase in viral concentration demonstrable. As viral multiplication ceased entirely, the non-multiplying virus was unable to persist in the lung, and disappearance of the virus began to occur within 48 hours of the single polysaccharide injection. As virus multiplication was inhibited and the quantity of non-multiplying virus was reduced in the lung, resolution of the pulmonary consolidation commenced. Results of other experiments indicate that the rapid diminution of non-multiplying virus is the result neither of the development of antibody nor the activity of the polysaccharide itself, but is due to some intrinsic mechanism of the lung.

The experiments described above clearly indicate that the course of an experimental viral pneumonia can be modified by polysaccharide so that complete recovery of mice may occur if therapy is instituted early enough to inhibit effectively viral multiplication. In effect then, polysaccharide appears able to temper the course of this viral pneumonia because it limits the concentration of PVM within the host cells to about that which is present at the time of injection of the substance, and thereby leads to quantitative reduction in the subsequent development of consolidation. That a single injection of a few micrograms of polysaccharide can so strikingly modify the normal course of this viral pneumonia seems to be further evidence in support of the hypothesis that the substance inhibits viral multiplication by acting primarily within susceptible host cells.

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[SECTION ON MICROBIOLOGY
continued on next page]

Further Experiments With Columbia Sk Murine Poliomyelitis Virus

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This presentation is a brief review of the pathology induced by infection with murine poliomyelitis virus in rodents and in monkeys. The strain under investigation is Columbia SK virus. The pathological data bear partly on the well-known morbid changes in the central nervous system, partly on certain less well-known alterations in the heart and skeletal muscle. In order to properly evaluate the significance of these lesions, reference will also be made to recent observations relating to the ability of freshly isolated human strains of poliomyelitis virus to induce similar central and peripheral lesions in experimental animals. In a sense, therefore, this communication is concerned with a problem of considerably greater magnitude, namely, definition of the virus and determination of the mechanism underlying the pathogenesis of the human disease.

It will be recalled that Col. SK virus shares in common certain fundamental properties with orthodox strains of murine poliomyelitis virus. These are: 1) production of flaccid paralysis in rodents with destructive lesions in the anterior horn; 2) intestinal infection with fecal excretion; 3) the characteristic, particle size (10-15 mu); 4) antigenic structure distinct from that of Theiler's virus of indigenous mouse encephalomyelitis (T.O., GDVII, F.A.). These data are so well corroborated that they may be accepted as established facts. On the other hand, significant differences exist with respect to several other biological properties, of which only the most important ones will be mentioned: 1) limited pathogenicity for rhesus monkeys, coupled with high virulence for rodents; 2) power to hemagglutinate sheep red cells and to grow in embryonated eggs; 3) ability to produce specific lesions in the heart and skeletal muscle during the course of the experimental infection; 4) antigenic structure distinct from that of certain other strains of mouse-adjusted human poliomyelitis virus (Lansing, Y-SK, MEF). These differences mark Col. SK virus and similar viruses, like MM, EMC and Mengo which are tentatively grouped together at present, as essentially pantropic agents and set them apart from the strictly neurotropic agents which until now have been identified as the typical virus of human poliomyelitis.[1] Nevertheless, some of this distinction is already being erased through the recent demonstration by Enders et al[2] that the Lansing strain, in tissue culture medium, multiplies as well on extraneural as on neural substrate.

Inasmuch as the problem before us is not to attempt a classification of the human disease but rather to evolve acceptable criteria for a definition of the etiological agent, this discussion will be limited to a brief characterization of the Col. SK group of viruses by laboratory procedures. A more detailed presentation of the entire subject will be found in a forthcoming review.[3] Obviously, the basic questions revolve around: 1) whether these viruses function as infecting agents in human populations, and 2) whether they are capable of inducing in monkeys what may be considered acute anterior poliomyelitis. In the event that these postulates should be met, there will then remain little doubt that the agent (or agents) which causes poliomyelitis—as the term is commonly understood on clinical, pathological and epidemiological grounds—occurs either in form of different phases of variation, or else that we are dealing with a heterogenous group of individually distinct though etiologically related viruses.

The available evidence which implicates the Col. SK group of viruses as potentially human-pathogenic agents is both direct and indirect. Thus, Mengo virus has been isolated from the blood of a human case of polioencephalomyelitis, acquired in all probability through laboratory infection.[4]

TABLE I

NEUTRALIZATION OF COL. SK VIRUS BY HUMAN POLIO-CONVALESCENT SERA (JERSEY CITY MEDICAL CENTER)

Year	Number of Sera	Neutralization Index			
		0	10-99	100-999	1000
1948	35	16	10	7	2
1949	91	59	15	12	5
1948-1949	126	75	25	19	7
	126	Neg: 100 (79%)		Pos: 26 (21%)	

COMPARISON OF COL. SK AND Y-SK VIRUS NEUTRALIZATION BY HUMAN POLIO-CONVALESCENT SERA

Sera	Number of Sera	Y-SK Virus Neutralization	
		Positive	Negative
Col. SK positive	21	16	5
Col. SK negative	46	30	16
Total	67	46 (68%)	21 (32%)

TABLE II

SUSCEPTIBILITY OF DIFFERENT SPECIES OF MONKEYS TO INFECTION WITH COL. SK VIRUS BY VARIOUS ROUTES

Monkey	Infection			
	i.c.	i.m.	i.p.	Gavage
Mac. cynomolgus	16/16	2/5	3/6	3/4
Cercopithecus	2/4		2/4	
Cebus capucinus	2/2			

i.c.: 10^{-1} 10^{-4}; i.m.: 10^{-1}; i.p.: 10^{-1} 10^{-2}; gavage: 10^{-1}.

That strains of the MM or EMC type of virus were responsible for an outbreak of so-called "three-day fever" (abortive poliomyelitis?) among American troops, stationed in Manila during the war,[5] may be inferred from the results of neutralization tests reported by Warren and Smadel.[6] Early attempts by us, in 1943, to demonstrate neutralization of Col. SK virus by human sera may be dismissed because of technical imperfection inherent in the procedure employed at that time.[7] However, the outbreak of 1948, and especially the extensive poliomyelitis epidemic of 1949 in Greater New York, afforded an opportunity to reinvestigate the problem. In these studies an accurately standardized quantitative technique was used and only sera from fresh cases of the disease were examined.[8] The results indicated that approximately 20 per cent of the sera from poliomyelitis patients, during the early stages of convalescence, contained sufficient antibodies against Col. SK virus to be listed as positive. This percentage is appreciably lower than that obtained in parallel tests against Yale SK virus which stands at approximately 70 per cent. However, the figures seem to imply a higher degree of serological specificity since Col. SK virus, unlike Yale SK virus, is but rarely neutralized by normal human sera. The fact that a majority of the Col. SK-positive sera were likewise positive for Y-SK virus is of additional interest (Table I).

Since pathogenicity for monkeys is generally considered to be one of the basic characteristics of human poliomyelitis virus, we have recently reëxamined the ability of the Col. SK group of murine viruses to produce frank paralysis in monkeys other than Mac. rhesus. It appeared from this work that Col. Sk, MM and EMC virus, following intracerebral injection into Mac. cynomolgus (Java) monkeys, induced in these animals, clinically as well as pathologically, the typical picture of experimental poliomyelitis.[9] These results in so far as Col. SK virus is concerned have meanwhile been confirmed by Verlinde.[10] Our studies were subsequently carried further to include a number of other Old and New World monkeys which were infected with Col. SK murine virus by neural and extraneural routes. The results are brought together in Table II. It will be seen that Col. SK virus, when introduced by a variety of channels of infection, is highly pathogenic for cynomolgus monkeys, producing uniformly typical flaccid paralysis with severe poliomyelitic lesions in the anterior horn (Fig. 1). Paralyzed cynomolgus monkeys often present, in addition, discrete foci of myocardial lesions. When the virus is injected intramuscularly there occurs a localized myositis in the paralyzed limb, accompanied by a segmental unilateral destruction of the anterior horn. The pathology in the skeletal muscle is similar to that

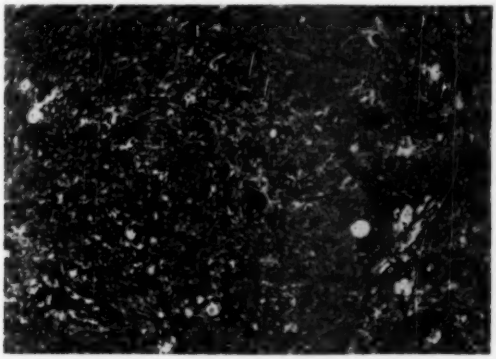

Fig. 1—Cynomolgus #150: Col. SK virus 10^{-1} i.c. Complete destruction of anterior horn with ganglion cell necrosis and slight perivascular infiltration.

described by Rustigian and Pappenheimer[11] in mice following intramuscular injection of Col. SK virus. The picture, on the whole, is not unlike the characteristic muscular lesion found with the Coxsackie type of virus.[12] Cercopithecus monkeys (African Green) apparently are somewhat less susceptible to paralytic involvement (Fig. 2) and their reaction begins to approach the subclinical response observed in rhesus

Fig. 2—Cercopithecus #2: Col. SK virus 10^{-2} i.c. Partial destruction of anterior horn with ganglion cell necrosis, neuronophagia and slight perivascular infiltration.

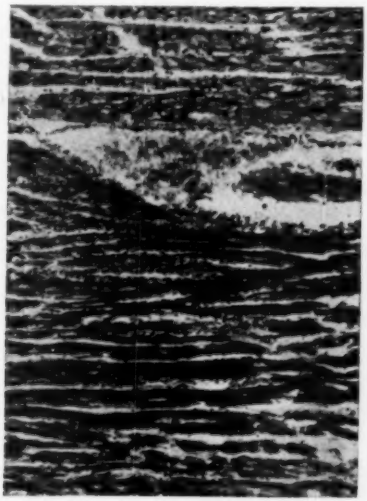

Fig. 3—Cercopithecus #4: Col. SK virus 10^{-2} i.p. Massive myocarditis with muscle fiber fragmentation and interstitial cell collections.

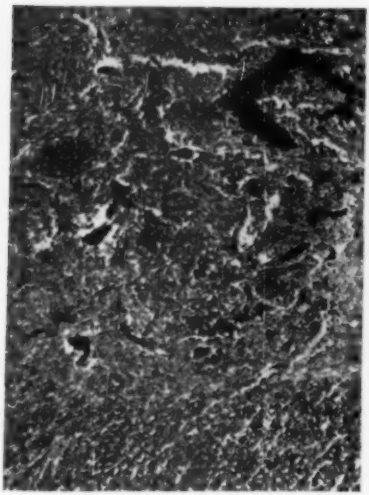

Fig. 4—Cynomolgus #111: F.A. virus (isolated from human paralyzed muscle) 10^{-1} i.c. Partial destruction of anterior horn with ganglion cell necrosis, neuronophagia and extensive perivascular infiltration.

Fig. 5—Cynomolgus #111: F.A. virus (isolated from human paralyzed muscle) 10^{-1} i.c. Focal myocarditis with muscle fiber necrosis and interstitial cellular reaction.

monkeys. It is noteworthy, however, that cercopithecus monkeys contract myocardial lesions with a frequency and severity hitherto not observed in any other experimental host (Fig. 3). There seems to be no simple relationship between the development of heart lesions and the development of central nervous system lesions, for myocarditis has also occurred in non-paralyzed monkeys which failed to show any anterior horn involvement. With Cebus capuchinus monkeys the observations are too few to permit any final conclusion but they suggest that Col. SK virus is also highly pathogenic for these animals. Corresponding differences in the susceptibility of various species of monkeys to infection with freshly isolated strains of human poliomyelitis virus have previously been reported by other authors.[12-16]

When the aforementioned observations are compared with what is known of the pathological manifestations in human and experimental poliomyelitis, agreement is easily attained with respect to the pathognomonic lesions in the central nervous system. However, as is generally known, most of the intracerebrally fixed neurotropic passage strains of virus fail to produce visceral lesions of the type characteristic for Col. SK virus. On the other hand, myocardial involvement seems to occur frequently in the human disease.[17] We have therefore reopened the problem: a) by studying the neural and extra-neural distribution of the virus in acute cases of the disease, b) by examining freshly isolated strains of human poliomyelitis virus for their ability to produce central and peripheral lesions in cynomolgus monkeys. Suffice it to say that, according to preliminary information, virus can be successfully isolated not only from the cord but also from the heart of fatal cases.[18] To this may be added that the virus has been recovered from the paralyzed muscle during the acute stage of the disease.[19] Upon further passage, such cord, heart or muscle strains were found capable of inducing in intracerebrally infected cynomolgus monkeys typical central nervous system lesions (Fig. 4) as well as peripheral lesions in the myocardium

TABLE III

PROPHYLACTIC EFFECT OF R.D.E. ON COL. SK INFECTION IN MICE.

Mice (10-12 *gms.*)	*Col. SK Infection*	*Number of Mice*	*Cumulative Mortality Days* 1-4	5	6	7	8	9-11	12	13	14	*Mortality Rate*	
RDE*	10^{-6} i.p.	20	0	0	4	5	7	7	8	8	8	8/20	40%
Controls**	10^{-6} i.p.	20	0	16	18	18	19	19	19	20		20/20	100%
"	10^{-7} i.p.	5	0	2	4	5						5/5	100%
"	10^{-8} i.p.	5	0	2	2	3	3	3	4	4	4	4/5	80%

* 2 cc. RDE (P&S cholera strain) given 5 hours before infection.

** 2cc. NaCl solution given 5 hours before infection.

REINFECTION EXPERIMENT (16 DAYS LATER)

Mice (20 *gms.*)	*Col. SK Infection*	*Number of Mice*	*Cumulative Mortality Days* 1-3	4	5	6	7-9	10	11-14	*Mortality Rate*	
RDE-treated survivors	10^{-4} i.p.	12	0	2	4	4	4	6	6	6/12	50%
Controls	10^{-4} i.p.	5	0	4	5					5/5	100%

(Fig. 5). The muscle strain, moreover, when passed by the intramuscular route, produced a severe myositis in the injected paralyzed leg, accompanied by a corresponding anterior horn lesion in the spinal cord. In other words, human poliomyelitis virus, isolated freshly from neural or extraneural tissues, appears to possess vicarious neurotropic and viscerotropic properties, duplicating in that respect the characteristic picture of Col. SK infection in monkeys and in rodents.[20]

If one accepts the fact that poliomyelitis virus may grow in muscle[2, 21] and, during that process, sets up an incipient local lesion, it becomes logical to pursue certain new chemical approaches to a study of the mechanism of paralysis and its possible control. For instance, an analysis of the distribution of Col. SK virus in the paralyzed muscle over isolated muscle proteins showed the virus to be present only in the myosin and not in the actin fraction.[22] The actomyosin. Measured by in vitro methods, responded to adenosine triphosphate with the contraction typical of normal actomyosin. Measured by in vitro methods, therefore, the lack of contractility of the paralyzed muscle does not seem to depend upon defects situated inside the actin-myosin-ATP system. This would place the dysfunction either with the acetylcholine-cholinesterase system or somewhere between the motor end-plate and muscle fiber. Another interesting problem concerns the possibilities of chemotherapeutic approach to an infection which conceivably begins peripherally and terminates centrally only after excessive accumulations of virus pass over the myoneural junction. The first successful step in that direction was recently taken by Verlinde[23] who could show that Burnet's[24] receptor-destroying enzyme (RDE), as extracted from cultures of *V. cholerae*, not only blocks hemagglutination in vitro but also protects mice against peripheral infection with Col. SK virus. We have repeated these experiments and observed similar protection. Table III gives the results obtained in a typical experiment.

SUMMARY AND CONCLUSIONS

The available evidence suggests that pantropic Col. SK virus produces in mon-

keys central and peripheral lesions similar to those observed with freshly isolated strains of human poliomyelitis virus. Since neurotropic standard strains, fixed by intracerebral passage, produce only the terminal neurological complication, which goes under the name of poliomyelitis acuta anterior, it follows that Col. SK virus reproduces more faithfully the human syndrome of Heine-Medin's disease. Inasmuch as the infectious process induced by Col. SK virus can be traced in its progression from the peripheral to the central motor neuron, this virus offers unusual opportunities for an experimental study of the pathogenesis of poliomyelitis. In view of the fact, finally, that Col. SK virus multiplies extraneurally, prior to invasion of the central nervous system, the experimental infection induced in monkeys or rodents by this virus provides an attractive model for chemotherapeutic investigations. From the data submitted emerges a new concept of the pathogenesis of poliomyelitis which holds a promise for better understanding of the human disease.

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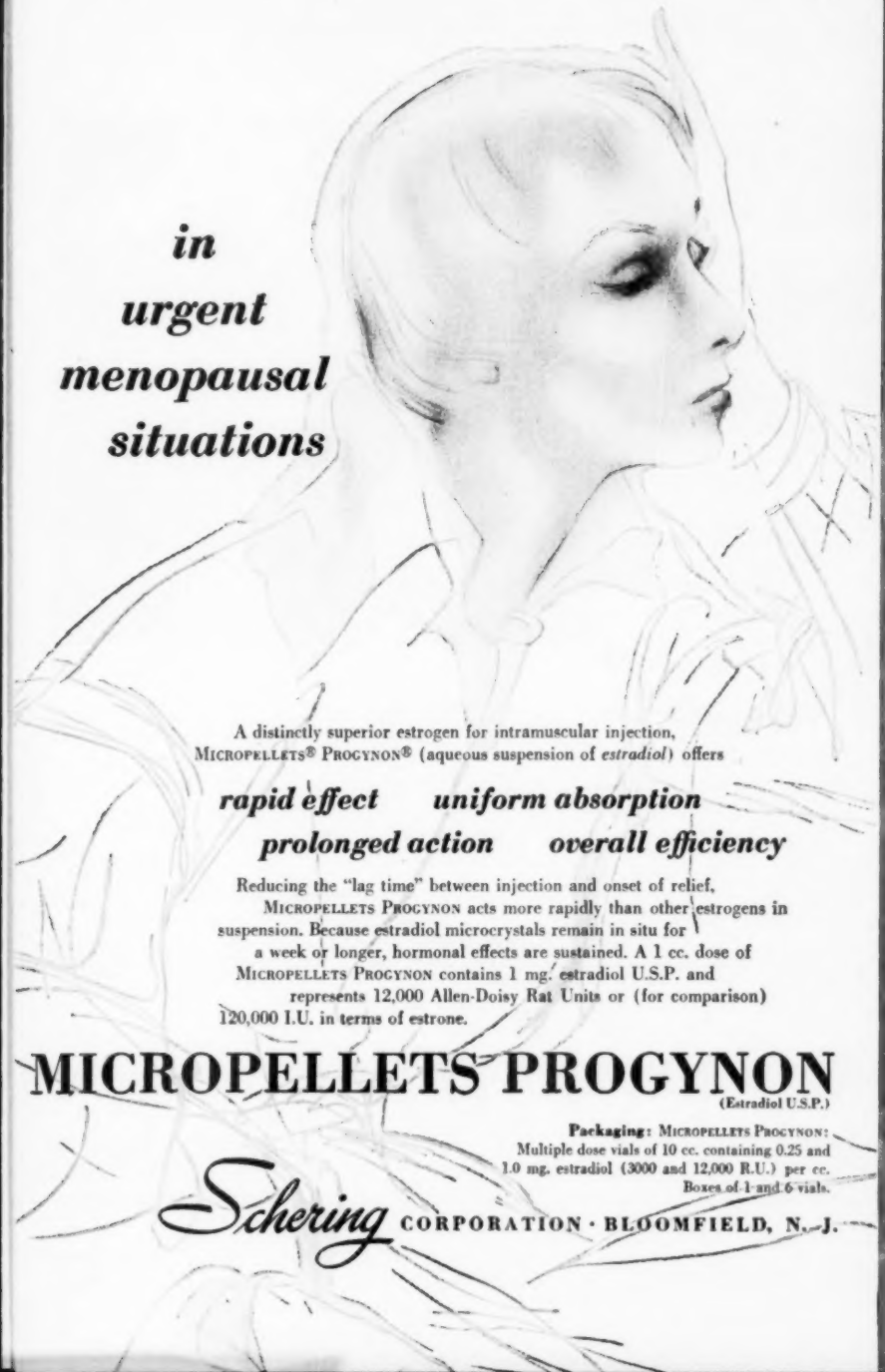

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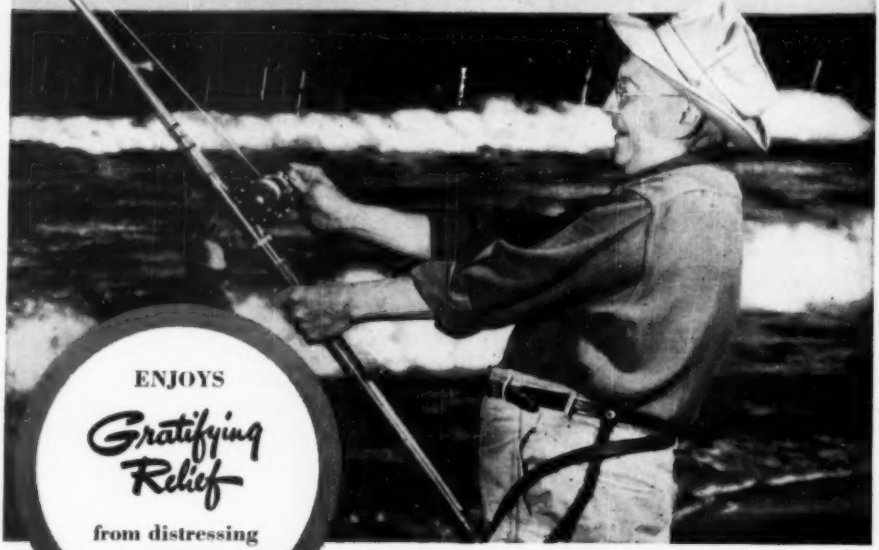

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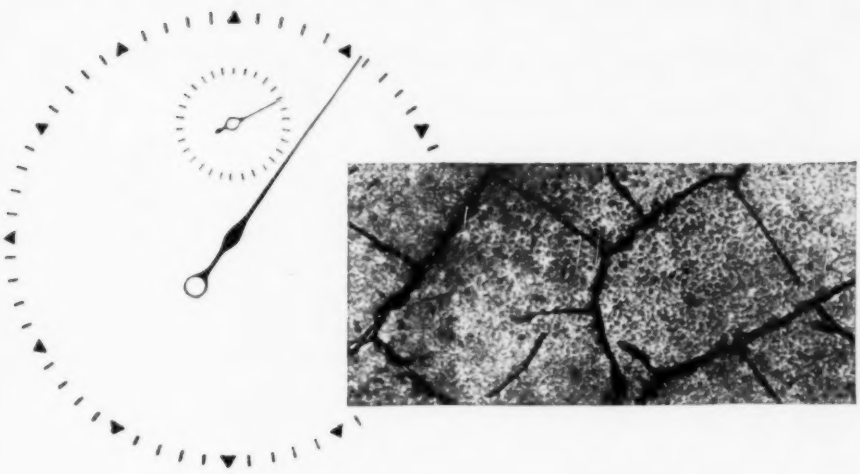

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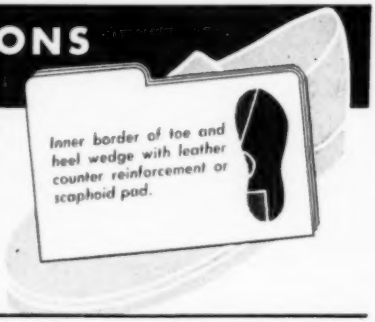

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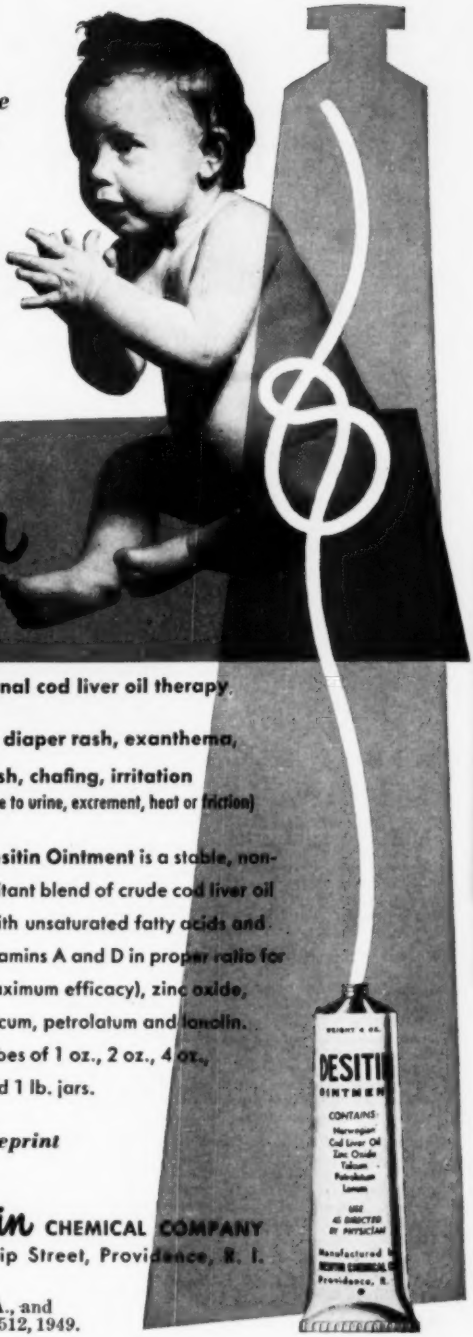

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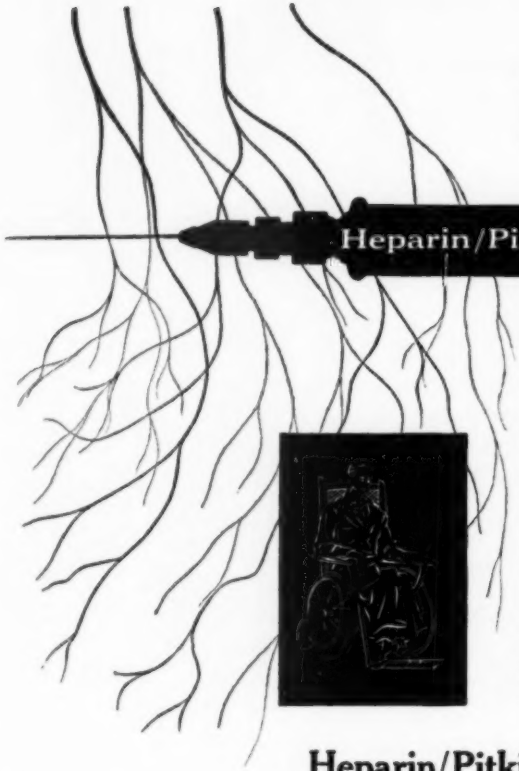

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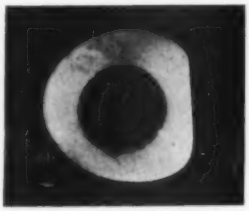

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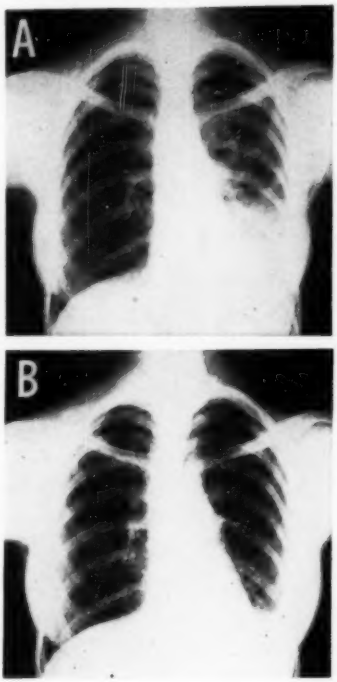

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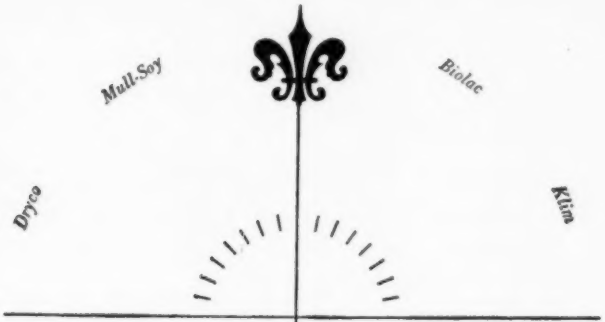

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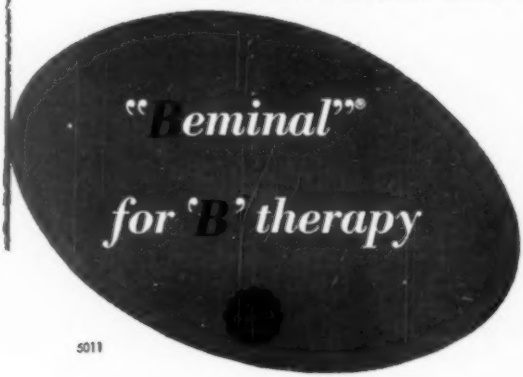

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